IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Ann-Kristin Karlsson *et al.*	Art Unit	: 1623
Serial No.	: 09/993,669	Examiner	: Leigh C. Maier
Filed	: November 27, 2001	Conf. No.	: 1605
Title	: STERILE POWDERS, FORMULATIONS AND METHODS OF PRODUCING THE SAME		

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF ANN-KRISTIN (KARLSSON) EKELUND UNDER 37 C.F.R. § 1.132

I, Ann-Kristin (Karlsson) Ekelund, hereby declare as follows:

1. I am a co-inventor on the above-captioned application. I have been employed at AstraZeneca and its predecessor companies since 1987. My present title is Project Manager. My Curriculum Vitae is attached as Exhibit A.

2. I understand that the U.S. Patent and Trademark Office Examiner in the above-referenced application has asserted that "it is reasonable to expect" that each of the AstraZeneca products Rhinocort Aqua® budesonide nasal spray mentioned in the abstract of Day et al. (Am J Rhinol 11:77-83, 1997) and Pulmicort Turbohaler®[2] budesonide inhalation powder mentioned in Jones et al. (Respir. Med. 88:293-299, 1994) was sold as a "sterile product," and also that "it is reasonable to expect" that these products utilized the 22R epimer of budesonide because it is the "more potent epimer." None of these expectations is borne out by the facts.

[1] Prior to a merger between Astra AB and Zeneca Group PLC in 1999, the products were manufactured and marketed by AstraZeneca's predecessor in interest, Astra AB. For simplicity, I use only the current name, AstraZeneca, to refer to the company both before and after the merger.

[2] Turbohaler® and Turbuhaler® are AstraZeneca trademarks used for the same product.

3. AstraZeneca manufactures and sells Rhinocort Aqua® nasal spray, which contains an aqueous suspension of budesonide particles, and Pulmicort Turbohaler® dry powder inhaler, which contains budesonide in the form of a dry powder.

4. The budesonide in the Rhinocort Aqua® and Pulmicort Turbohaler® products is a racemic mixture of both the 22R and 22S enantiomers of budesonide. See the paragraph headed "DESCRIPTION" in the AstraZeneca product descriptions for these products attached as Exhibits B and C, respectively, where the budesonide is described as "(RS)" (denoting a mixture of the R and S enantiomers), followed by the chemical name. While these product descriptions are both post-1997 (see the date at the end of each document), the budesonide used in the products has not changed and was always the racemic mixture. Exhibit D is a 1995 Specification for micronized budesonide prepared for use in the Rhinocort Aqua® nasal spray product. It states "Budesonide is a mixture of two epimeric forms, epimer A and epimer B." (Epimers A and B correspond to the 22R and 22S enantiomers.) Similarly, Exhibit E is a 1997 Specification for budesonide prepared for use in the Pulmicort Turbuhaler® product. It carries the same statement.

5. Prior to the November 1997 priority date of the present application, and continuing to today, neither the Rhinocort Aqua® product nor the Pulmicort Turbohaler® product has been sterilized prior to sale by AstraZeneca, and neither has been sold labeled as a "sterile" product.

6. In general, sterility of pharmaceutical products is determined in accordance with the criteria described in the US Pharmacopeia 23/NF18, 1995, pages 1686-1690 (also referred to as "USP <71>") and 1963-1975 ("USP <1206>"). A copy of these sections of the US Pharmacopeia is attached as Exhibit F. These are the portions of the US Pharmacopeia that are referenced in the definition of "sterile" in the present application at page 7, lines 6-7, and also referenced in certain of the claims as presently amended. The product quality specification filed by a manufacturer with the US Food and Drug Administration (FDA) for a pharmaceutical product that is to be labeled as "sterile" includes as one requirement something to the effect that

the product "meets current USP <71>," meaning that it has been tested in accordance with the US Pharmacopeia 23/NF18 and has met the criteria in that document. See, e.g., the category "Sterility" at the end of the current "Specification for Pulmicort Respules" attached as Exhibit G. (Pulmicort Respules® budesonide inhalation suspension, another AstraZeneca budesonide product, is discussed further below.)

7. The product quality specifications for non-sterilized products such as Rhinocort Aqua® and Pulmicort Turbuhaler® do not mention "sterility" at all, and instead merely require that the product have microbial counts under specified limits in accordance with a different section of the US Pharmacopeia, USP <61> (copy attached as Exhibit H). See, e.g., the "Microbial quality" category at the end of the 17 September 1997 Specification for PULMICORT 200 TURBUHALER attached as Exhibit I and the "Microbiological condition" category at the end of the 25 April 1991 Specification for RHINOCORT nasal spray attached as Exhibit J. The USP <61> tests that are used to determine whether the microbial counts are under the required limits do not give a readout that FDA recognizes as "sterile." Unless the USP <71> tests are used, there is no way to determine whether any given batch of a product in fact qualifies as "sterile" under USP <71>.

8. In 2001, FDA issued a Guidance for Industry (see Exhibit K), in which manufacturers were informed that as of May 27, 2002, all aqueous-based drug products for oral inhalation must be manufactured sterile. The answer to the first question on page 2 of that Guidance indicates that nasal spray drug products are specifically exempted from the requirement. Rhinocort Aqua® is a nasal spray drug product. Thus, the Guidance provides evidence consistent with the fact that FDA does not require that Rhinocort Aqua® be manufactured sterile. The Guidance does not mention inhalable dry powder drug products, but in fact FDA also has not required that Pulmicort Turbuhaler® be manufactured sterile.

9. As mentioned above, the AstraZeneca product Pulmicort Respules® budesonide oral inhalation suspension (on the market in the U.S. since 2000) is presently marketed as a sterile product. See Exhibit G (last line) and also the Pulmicort Respules® product information

dated 06/07 enclosed as Exhibit L, which in the first column of the first page describes the product as follows: "PULMICORT RESPULES is a sterile suspension for inhalation... ." A similar product was marketed outside the U.S. before the November 1997 priority date of the present application, *but not in a sterilized form*. (See the Pulmicort® Suspension for Nebulizing product specification dated February 23, 1994, enclosed as Exhibit M, which lists a "Microbiological condition" requirement instead of a "Sterility" requirement.) When AstraZeneca proposed to market this unsterilized oral inhalation suspension product in the US, AstraZeneca was informed by FDA that FDA was moving toward requiring that this particular type of product, i.e., aqueous-based drug products for oral inhalation, be manufactured sterile. I attended a pre-NDA meeting[3] between AstraZeneca and the FDA on November 20, 1996, to discuss the proposed Pulmicort Respules® product. As recorded in the minutes of that meeting (attached hereto as Exhibit N), AstraZeneca described to the FDA the problems encountered when experimental attempts were made to sterilize budesonide, both as a suspension and as a dry powder. See the carryover paragraph of pages 2-3 of the Exhibit N minutes. Subsequent to this meeting, AstraZeneca experimented further to find an acceptable method of sterilizing budesonide, ultimately resulting in the novel method I and my co-inventors discovered and disclosed in the present patent application. This sterilization method is now used in the manufacture of sterile Pulmicort Respules®. It was not used by AstraZeneca in any budesonide product sold before the November 1997 priority date.

10. Both Pulmicort Respules® and its unsterilized predecessor product Pulmicort® suspension for nebulizing contain budesonide in the form of a racemic mixture.

11. In contrast to the statement quoted above from the Pulmicort Respules® 06/07 product information (Exhibit L), which explicitly describes the product as "sterile," recent product information sheets for Rhinocort Aqua® (Exhibit B; dated 01/05) and Pulmicort Turbuhaler® (Exhibit C; dated 10/06) do not mention sterility. If the latter two products were

[3] A "pre-NDA meeting" is a meeting prior to submission of a New Drug Application for review by the FDA.

manufactured sterile, they would normally be described as "sterile" in the product information sheets, just as is Pulmicort Respules®.

12. Page 2 of Exhibit N contains a statement attributed to a Dr. Ng of the FDA that "the product is labeled sterile, however it is has not been sterilized." Since the Pulmicort® suspension product under discussion at that meeting at that time had been sold only outside the U.S. and only in an unsterilized form, and certainly would not have been labeled "sterile" if it had not been sterilized, the basis for this statement is not clear. It may have been related to a showing of no bacterial growth in the product, discussed later in the same paragraph.

13. Page 3 of Exhibit N contains a statement attributed to a Dr. Poochikian of the FDA that "in general we expect inhalation products to be sterile." Since there was at the time of the meeting no FDA requirement that either (a) suspensions for nasal inhalation or (b) dry powder inhalation products be sterile (and still is no such requirement), Dr. Poochikian was probably referring solely to aqueous-based drug products for oral inhalation, the particular type of product under discussion at the meeting. As noted above, FDA informed AstraZeneca that FDA was moving toward making it a requirement that aqueous-based drug products for oral inhalation be sterile; this requirement was formalized in the 2001 Guidance for Industry (Exhibit K) discussed above.

14. Several years ago, AstraZeneca marketed Preferid® cream, a topical cream (not for inhalation) containing particles of budesonide (in the form of a racemate) suspended in a cream base formed of oil-in-water. During the period of about 1980 to about 1983, the manufacturing process for the Preferid® product marketed in the Scandinavian countries included a step of exposing the budesonide particles to ethylene oxide gas prior to combination with the cream base to form the Preferid® cream. A specification from 1983 (Exhibit O) describes the ethylene oxide-treated, micronized budesonide produced for use in Preferid® cream as "sterile according to Ph.Eur" (see last page). The manufacturing method for this product is described in a document dated September 9, 1980 (Swedish original and English translation attached as Exhibit P). Around 1983, changes in the regulatory requirements for this

product in the Scandinavian countries led to abandonment of the ethylene oxide exposure step and removal of the term "sterile" from the product description for Preferid® cream.

15. By 1997, it was understood in the pharmaceutical arts that a budesonide powder composition that had been exposed to ethylene oxide gas in an effort to sterilize it would not be considered "pharmaceutically acceptable" because of the possibility that residual ethylene oxide gas molecules remain in the product.

16. While ethylene oxide gas can kill microorganisms that are on the surface of crystalline particles, there is no assurance it can penetrate into the crystal core of a particle to reach microorganisms encased in the crystal core. See page 6 of "Guide to Inspection of Sterile Drug Substance Manufacturers," a printout from the FDA website (www.fda.gov/ora/inspect_ref/igs/iglist.html) that was submitted as reference AL in the Information Disclosure Statement filed June 26, 2006, and is also attached hereto as Exhibit Q. This 1994 FDA document notes that "As a primary means of sterilization, [ethylene oxide's] utilization is questionable because of lack of assurance of penetration into the crystal core of a sterile powder." See also Mullican and Hoffman, Applied Microbiology 16:1110-1113, 1968, submitted as reference AM in the same Information Disclosure Statement and attached hereto as Exhibit R. Mullican and Hoffman reported that ethylene oxide does not decrease the count of viable bacterial spores encased inside intact crystals of either NaCl or glycine.

17. Exhibit S is an internal Draco[4] document dated March 26, 1980. Exhibit T is an internal Draco document dated November 4, 1980. Exhibits U1-U11 are eleven single-page internal Draco documents variously dated from 14 September 1978 to 28 August 1980, all in Swedish with an English translation attached.

18. I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these

[4] Draco was a subsidiary of Astra AB.

statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

9 Sept 2008
Date

Ann-Kristin (Karlsson) Ekelund

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AstraZeneca

Curriculum Vitae

FULL NAME:	Ekelund, Mari Ann-Kristin Elisabeth (née Karlsson)
DATE OF BIRTH:	22 September 1961
CITIZENSHIP:	Swedish
PRESENT POSITION:	Project Manager, Project Management, PAR&D, AstraZeneca R&D Lund, 1 July 2006-
EDUCATION:	MSc in Chemical Engineering, 1986
PREVIOUS POSITION:	Research Technician, Analytical Chemistry, AB Draco, Lund, 1987-1991 Research Scientist, Analytical Chemistry, Astra Draco AB, Lund, 1991-1993 Assistant Director, Analytical Chemistry, Astra Draco AB, Lund, 1993-1997 Assistant Director, Analysis - Formulations, Astra Draco AB, Lund, 1997-1999 Associate Director, Nasals/Nebules & Drug Substance, AstraZeneca R&D Lund, 1999-2000 Team Manager, Analytical Development 2, AstraZeneca R&D Lund, 2000-2001 Manager, Analytical Development 2, AstraZeneca R&D Lund, 2001-2006
PUBLICATIONS:	
CURRENT MEMBERSHIP OF PROFESSIONAL ASSOCIATIONS:	
DATE OF ISSUE:	28 Sept 2006
SIGNATURE:	
INITIALS:	akk AKK

RHINOCORT AQUA®

(budesonide)

Nasal Spray 32 mcg

For Intranasal Use Only.

Rx only

DESCRIPTION

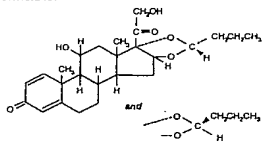
Budesonide, the active ingredient of RHINOCORT AQUA® Nasal Spray, is an anti-inflammatory synthetic corticosteroid.

It is designated chemically as (RS)-11-beta, 16-alpha, 17, 21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16, 17-acetal with butyraldehyde.

Budesonide is provided as the mixture of two epimers (22R and 22S).

The empirical formula of budesonide is $C_{25}H_{34}O_6$ and its molecular weight is 430.5.

Its structural formula is:



Budesonide is a white to off-white, odorless powder that is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform.

Its partition coefficient between octanol and water at pH 5 is 1.6×10^3.

RHINOCORT AQUA is an unscented, metered-dose, manual-pump spray formulation containing a micronized suspension of budesonide in an aqueous medium. Microcrystalline cellulose and carboxymethyl cellulose sodium, dextrose anhydrous, polysorbate 80, disodium edetate, potassium sorbate, and purified water are contained in this medium; hydrochloric acid is added to adjust the pH to a target of 4.5.

RHINOCORT AQUA Nasal Spray delivers 32 mcg of budesonide per spray.

Each bottle of RHINOCORT AQUA Nasal Spray 32 mcg contains 120 metered sprays after initial priming.

Prior to initial use, the container must be shaken gently and the pump must be primed by actuating eight times. If used daily, the pump does not need to be reprimed. If not used for two consecutive days, reprime with one spray or until a fine spray appears. If not used for more than 14 days, rinse the applicator and reprime with two sprays or until a fine spray appears.

CLINICAL PHARMACOLOGY

Budesonide is a synthetic corticosteroid having potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay. In glucocorticoid receptor affinity studies, the 22R form was twice as active as the 22S epimer.

The precise mechanism of corticosteroid actions in seasonal and perennial allergic rhinitis is not known. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (eg, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (eg, histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic mediated inflammation.

Corticosteroids affect the delayed (6 hour) response to an allergen challenge more than the histamine-associated immediate response (20 minute). The clinical significance of these findings is unknown.

Pharmacokinetics

The pharmacokinetics of budesonide have been studied following nasal, oral, and intravenous administration. Budesonide is relatively well absorbed after both inhalation and oral administration, and is rapidly metabolized into metabolites with low corticosteroid potency. The clinical activity of RHINOCORT AQUA Nasal Spray is therefore believed to be due to the parent drug, budesonide. *In vitro* studies indicate that the two epimeric forms of budesonide do not interconvert.

Absorption

Following intranasal administration of RHINOCORT AQUA, the mean peak plasma concentration occurs at approximately 0.7 hours. Compared to an intravenous dose, approximately 34% of the delivered intranasal dose reaches the systemic circulation, most of which is absorbed through the nasal mucosa. While budesonide is well absorbed from the GI tract, the oral bioavailability of budesonide is low (~10%) primarily due to extensive first pass metabolism in the liver.

Distribution

Budesonide has a volume of distribution of approximately 2-3 L/kg. The volume of distribution for the 22R epimer is almost twice that of the 22S epimer. Protein binding of budesonide *in vitro* is constant (85–90%) over a concentration range (1-100 nmol/L) which exceeded that achieved after administration of recommended doses. Budesonide shows little to no binding to glucocorticosteroid binding globulin. It rapidly equilibrates with red blood cells in a concentration independent manner with a blood/plasma ratio of about 0.8.

Metabolism

Budesonide is rapidly and extensively metabolized in humans by the liver. Two major metabolites (16α-hydroxyprednisolone and 6β-hydroxybudesonide) are formed via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4)-catalyzed biotransformation. Known metabolic inhibitors of (CYP3A4) (eg, ketoconazole), or significant hepatic impairment, may increase the systemic exposure of unmetabolized budesonide (see WARNINGS and PRECAUTIONS). *In vitro* studies on the binding of the two primary metabolites to the glucocorticoid receptor indicate that they have less than 1% of the affinity for the receptor as the parent compound budesonide. *In vitro* studies have evaluated sites of metabolism and showed negligible metabolism in skin, lung, and serum. No qualitative difference between the *in vitro* and *in vivo* metabolic patterns could be detected.

Elimination

Budesonide is excreted in the urine and feces in the form of metabolites. After intranasal administration of a radiolabeled dose, 2/3 of the radioactivity was found in the urine and the remainder in the feces. The main metabolites of budesonide in the 0-24 hour urine sample following IV administration are 16α-hydroxyprednisolone (24%) and 6β-hydroxybudesonide (5%). An additional 34% of the radioactivity recovered in the urine was identified as conjugates.

The 22R form was preferentially cleared with clearance value of 1.4 L/min vs. 1.0 L/min for the 22S form. The terminal half-life, 2 to 3 hours, was similar for both epimers and it appeared to be independent of dose.

Special Populations

Geriatric: No specific pharmacokinetic study has been undertaken in subjects >65 years of age.

Pediatric: After administration of RHINOCORT AQUA Nasal Spray, the time to reach peak drug concentrations and plasma half-life were similar in children and in adults. Children had plasma concentrations approximately twice those observed in adults due primarily to differences in weight between children and adults.

Gender: No specific pharmacokinetic study has been conducted to evaluate the effect of gender on budesonide pharmacokinetics. However, following administration of 400 mcg of RHINOCORT AQUA Nasal Spray to 7 male and 8 female volunteers in a pharmacokinetic study, no major gender differences in the pharmacokinetic parameters were found.

Race: No specific study has been undertaken to evaluate the effect of race on budesonide pharmacokinetics.

Renal Insufficiency: The pharmacokinetics of budesonide have not been investigated in patients with renal insufficiency.

Hepatic Insufficiency: Reduced liver function may affect the elimination of corticosteroids. The pharmacokinetics of orally administered budesonide were affected by compromised liver function as evidenced by a doubled systemic availability. The relevance of this finding to intranasally administered budesonide has not been established.

Pharmacodynamics

A 3-week clinical study in seasonal rhinitis, comparing RHINOCORT Nasal Inhaler, orally ingested budesonide, and placebo in 98 patients with allergic rhinitis due to birch pollen, demonstrated that the therapeutic effect of RHINOCORT Nasal Inhaler can be attributed to the topical effects of budesonide.

The effects of RHINOCORT AQUA Nasal Spray on adrenal function have been evaluated in several clinical trials. In a four-week clinical trial, 61 adult patients who received 256 mcg daily of RHINOCORT AQUA Nasal Spray demonstrated no significant differences from patients receiving placebo in plasma cortisol levels measured before and 60 minutes after 0.25 mg intramuscular cosyntropin. There were no consistent differences in 24-hour urinary cortisol measurements in patients receiving up to 400 mcg daily. Similar results were seen in a study of 150 children and adolescents aged 6 to 17 with perennial rhinitis who were treated with 256 mcg daily for up to 12 months.

After treatment with the recommended maximal daily dose of RHINOCORT AQUA (256 mcg) for seven days, there was a small, but statistically significant decrease in the area under the plasma cortisol-time curve over 24 hours ($AUC_{0\text{-}24h}$) in healthy adult volunteers.

A dose-related suppression of 24-hour urinary cortisol excretion was observed after administration of RHINOCORT AQUA doses ranging from 100–800 mcg daily for up to four days in 78 healthy adult volunteers. The clinical relevance of these results is unknown.

Clinical Trials

The therapeutic efficacy of RHINOCORT AQUA Nasal Spray has been evaluated in placebo-controlled clinical trials of seasonal and perennial allergic rhinitis of 3–6 weeks duration.

The number of patients treated with budesonide in these studies was 90 males and 51 females aged 6–12 years and 691 males and 694 females 12 years and above. The patients were predominantly Caucasian.

Overall, the results of these clinical trials showed that RHINOCORT AQUA Nasal Spray administered once daily provides statistically significant reduction in the severity of nasal symptoms of seasonal and perennial allergic rhinitis including runny nose, sneezing, and nasal congestion.

An improvement in nasal symptoms may be noted in patients within 10 hours of first using RHINOCORT AQUA Nasal Spray. This time to onset is supported by an environmental exposure unit study in seasonal allergic rhinitis patients which demonstrated that RHINOCORT AQUA Nasal Spray led to a statistically significant improvement in nasal symptoms compared to placebo by 10 hours. Further support comes from a clinical study of patients with perennial allergic rhinitis which demonstrated a statistically significant improvement in nasal symptoms for both RHINOCORT AQUA Nasal Spray and for the active comparator (mometasone furoate) compared to placebo by 8 hours. Onset was also assessed in this study with peak nasal inspiratory flow rate and this endpoint failed to show efficacy for either active treatment. Although statistically significant improvements in nasal symptoms compared to placebo were noted within 8–10 hours in these studies, about one half to two thirds of the ultimate clinical improvement with RHINOCORT AQUA Nasal Spray occurs over the first 1–2 days, and maximum benefit may not be achieved until approximately 2 weeks after initiation of treatment.

INDICATIONS AND USAGE

RHINOCORT AQUA Nasal Spray is indicated for the management of nasal symptoms of seasonal or perennial allergic rhinitis in adults and children six years of age and older.

CONTRAINDICATIONS

Hypersensitivity to any of the ingredients in this preparation contraindicates the use of RHINOCORT AQUA Nasal Spray.

WARNINGS

The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency, and in addition some patients may experience symptoms of corticosteroid withdrawal, eg, joint and/or muscular pain, lassitude, and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Patients who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on immunosuppressant doses of corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information). If chicken pox develops, treatment with antiviral agents may be considered.

PRECAUTIONS

General

Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see PRECAUTIONS, Pediatric Use).

Rarely, immediate and/or delayed hypersensitivity reactions may occur after the intranasal administration of budesonide. Rare instances of wheezing, nasal septum perforation, and increased intraocular pressure have been reported following the intranasal application of corticosteroids, including budesonide.

Although systemic effects have been minimal with recommended doses of RHINOCORT AQUA Nasal Spray, any such effect is dose dependent. Therefore, larger than recommended doses of RHINOCORT AQUA Nasal Spray should be avoided and the minimal effective dose for the patient should be used (see DOSAGE and ADMINISTRATION). When used at larger doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, the dosage of RHINOCORT AQUA Nasal Spray should be discontinued slowly, consistent with accepted procedures for discontinuing oral corticosteroid therapy.

In clinical studies with budesonide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local or systemic therapy and discontinuation of treatment with RHINOCORT AQUA Nasal Spray. Patients using RHINOCORT AQUA Nasal Spray over several months or longer should be examined periodically for evidence of *Candida* infection or other signs of adverse effects on the nasal mucosa.

RHINOCORT AQUA Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculous infection, untreated fungal, bacterial, or systemic viral infections, or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or nasal trauma should not use a nasal corticosteroid until healing has occurred.

Hepatic dysfunction influences the pharmacokinetics of budesonide, similar to the effect on other corticosteroids, with a reduced elimination rate and increased systemic availability (see CLINICAL PHARMACOLOGY, Special Populations).

Information for Patients

Patients being treated with RHINOCORT AQUA Nasal Spray should receive the following information and instructions. Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles and, if exposed, to obtain medical advice.

Patients should use RHINOCORT AQUA Nasal Spray at regular intervals since its effectiveness depends on its regular use (see DOSAGE AND ADMINISTRATION).

An improvement in nasal symptoms may be noted in patients within 10 hours of first using RHINOCORT AQUA Nasal Spray. This time to onset is supported by an environmental exposure unit study in seasonal allergic rhinitis patients which demonstrated that RHINOCORT AQUA Nasal Spray led to a statistically significant improvement in nasal symptoms compared to placebo by 10 hours. Further support comes from a clinical study of patients with perennial allergic rhinitis which demonstrated a statistically significant improvement in nasal symptoms for both RHINOCORT AQUA Nasal Spray and for the active comparator (mometasone furoate) compared to placebo by 8 hours. Onset was also assessed in this study with peak nasal inspiratory flow rate and this endpoint failed to show efficacy for either active treatment. Although statistically significant improvements in nasal symptoms compared to placebo were noted within 8–10 hours in these studies, about one half to two thirds of the ultimate clinical improvement with RHINOCORT AQUA Nasal Spray occurs over the first 1–2 days, and maximum benefit may not be achieved until approximately 2 weeks after initiation of treatment. Initial assessment for response should be made during this time frame and periodically until the patient's symptoms are stabilized.

The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve after two weeks, or if the condition worsens. Patients who experience recurrent episodes of epistaxis (nosebleeds) or nasal septum discomfort while taking this medication should contact their physician. For proper use of this unit

and to attain maximum improvement, the patient should read and follow the accompanying patient instructions carefully.

It is important to shake the bottle well before each use. The RHINOCORT AQUA Nasal Spray 32 mcg bottle has been filled with an excess to accommodate the priming activity. The bottle should be discarded after 120 sprays following initial priming, since the amount of budesonide delivered per spray thereafter may be substantially less than the labeled dose. Do not transfer any remaining suspension to another bottle.

Drug Interactions

The main route of metabolism of budesonide, as well as other corticosteroids, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a potent inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased by more than sevenfold. Concomitant administration of other known inhibitors of CYP3A4 (eg, itraconazole, clarithromycin, erythromycin, etc.) may inhibit the metabolism of, and increase the systemic exposure to, budesonide (see WARNINGS and PRECAUTIONS, General). Care should be exercised when budesonide is coadministered with long-term ketoconazole and other known CYP3A4 inhibitors.

Omeprazole, an inhibitor of CYP2C19, did not have effects on the pharmacokinetics of oral budesonide, while cimetidine, primarily an inhibitor of CYP1A2, caused a slight decrease in budesonide clearance and corresponding increase in its oral bioavailability.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in the male rats receiving an oral dose of 50 mcg/kg (approximately twice the maximum recommended daily intranasal dose in adults and children on a mcg/m² basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 mcg/kg (approximately equal to and two times the maximum recommended daily intranasal dose in adults and children on a mcg/m² basis, respectively). In two additional two-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (approximately twice the maximum recommended daily intranasal dose in adults and children on a mcg/m² basis). However, in male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (approximately twice the maximum recommended daily intranasal dose in adults and children on a mcg/m² basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings.

In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (approximately 3 times the maximum recommended daily intranasal dose in adults and children on a mcg/m² basis).

Budesonide was not mutagenic or clastogenic in six different test systems: Ames *Salmonella*/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in *Drosophila melanogaster*, and DNA repair analysis in rat hematocyte culture.

In rats, budesonide caused a decrease in prenatal viability and viability of the pups at birth and during lactation, along with a decrease in maternal bodyweight gain, at subcutaneous doses of 20 mcg/kg and above (less than the maximum recommended daily intranasal dose in adults on a mcg/m² basis). No such effects were noted at 5 mcg/kg (less than the maximum recommended daily intranasal dose in adults on a mcg/m² basis).

Pregnancy

Teratogenic Effects: Pregnancy Category B: The impact of budesonide on human pregnancy outcomes has been evaluated through assessments of birth registries linked with maternal usage of inhaled budesonide (ie, PULMICORT TURBUHALER) and intranasally administered budesonide (ie, RHINOCORT AQUA Nasal Spray). The results from population-based prospective cohort epidemiological studies reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-2001 (ie, Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry) indicate no increased risk for overall congenital malformations from the use of inhaled or intranasal budesonide during early pregnancy.

Congenital malformations were studied in 2,014 infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 10-12 weeks after the last menstrual period), the period when most major organ malformations occur.[1] The rate of overall congenital malformations was similar compared to the general population rate (3.8 % vs. 3.5%, respectively). The number of infants born with orofacial clefts and cardiac defects was similar to the expected number in the general population (4 children vs. 3.3 and 18 children vs. 17-18, respectively). In a follow-on study bringing the total number of infants to 2,534, the rate of overall congenital malformations among infants whose mothers were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%).[2] A third study from the Swedish Medical Birth Registry of 2,968 pregnancies exposed to inhaled budesonide, the majority of which were first trimester exposures, reported gestational age, birth weight, birth length, stillbirths, and multiple births similar for exposed infants compared to nonexposed infants.[3]

Congenital malformations were studied in 2,113 infants born to mothers reporting the use of intranasal budesonide in early pregnancy. The rate of overall congenital malformations was similar compared to the general population rate (4.5% vs. 3.5%, respectively). The adjusted odds ratio (OR) was 1.06 (95% CI 0.86-1.31). The number of infants born with orofacial clefts was similar to the expected number in the general population (3 children vs. 3, respectively). The number of infants born with cardiac defects exceeded that expected in the general population (28 children vs. 17.8 respectively). The systemic exposure from intranasal budesonide is 6-fold less than from inhaled budesonide and an association of cardiac defects was not seen with higher exposures of budesonide.

As with other corticosteroids, budesonide was teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weights, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg in rabbits and 500 mcg/kg in rats (approximately 2 and 16 times the maximum recommended daily intranasal dose in adults on a mcg/m² basis). In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 250 mcg/kg (approximately 8 times the maximum recommended daily intranasal dose in adults on a mcg/m² basis).

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is an increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Despite the animal findings, it would appear that the possibility of fetal harm is remote if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, RHINOCORT AQUA should be used during pregnancy only if clearly needed.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers

It is not known whether budesonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when RHINOCORT AQUA Nasal Spray is administered to nursing women.

Pediatric Use

Safety and effectiveness in pediatric patients below 6 years of age have not been established.

Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA)-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including RHINOCORT AQUA Nasal Spray, should be monitored routinely (eg, via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of safe and effective noncorticosteroid treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, including RHINOCORT AQUA Nasal Spray, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

A one-year placebo-controlled clinical growth study was conducted in 229 pediatric patients (ages 4 through 8 years of age) to assess the effect of RHINOCORT AQUA (single-daily dose of 64 mcg, the recommended starting dose for children ages 6 years and above) on growth velocity. From a population of 141 patients receiving RHINOCORT AQUA Nasal Spray and 67 receiving placebo, the point estimate for growth velocity with RHINOCORT AQUA Nasal Spray was 0.25 cm/year lower than that noted with placebo (95% confidence interval ranging from 0.59 cm/year lower than placebo to 0.08 cm/year higher than placebo).

The potential for RHINOCORT AQUA to cause growth suppression in susceptible patients or when given at doses above 64 mcg daily cannot be ruled out. The recommended dosage range in patients 6 to 11 years of age is 64 to 128 mcg per day (see DOSAGE AND ADMINISTRATION).

Geriatric Use

Of the 2,461 patients in clinical studies of RHINOCORT AQUA Nasal Spray, 5% were 60 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, except for an adverse event reporting frequency of epistaxis which increased with age. Further, other reported clinical experience has not identified any other differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

The incidence of common adverse reactions is based upon two U.S. and five non-U.S. controlled clinical trials in 1,526 patients [110 females and 239 males less than 18 years of age, and 635 females and 542 males 18 years of age and older] treated with RHINOCORT AQUA Nasal Spray at doses up to 400 mcg once daily for 3-6 weeks. The table below describes adverse events occurring at an incidence of 2% or greater and more common among RHINOCORT AQUA Nasal Spray-treated patients than in placebo-treated patients in controlled clinical trials. The overall incidence of adverse events was similar between RHINOCORT AQUA and placebo.

Adverse Event	RHINOCORT AQUA	Placebo Vehicle
Epistaxis	8%	5%
Pharyngitis	4%	3%
Bronchospasm	2%	1%
Coughing	2%	<1%
Nasal Irritation	2%	<1%

A similar adverse event profile was observed in the subgroup of pediatric patients 6 to 12 years of age.

Two to three percent (2-3%) of patients in clinical trials discontinued because of adverse events. Systemic corticosteroid side effects were not reported during controlled clinical studies with RHINOCORT AQUA Nasal Spray.

If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, ie, Cushing's Syndrome, could occur.

Rare adverse events reported from post-marketing experience include: nasal septum perforation, pharynx disorders (throat irritation, throat pain, swollen throat, burning throat, and itchy throat), angioedema, anosmia, and palpitations.

Cases of growth suppression have been reported for intranasal corticosteroids including RHINOCORT AQUA Nasal Spray (see PRECAUTIONS, Pediatric Use).

OVERDOSAGE

Acute overdosage with this dosage form is unlikely since one 120 spray bottle of RHINOCORT AQUA Nasal Spray 32 mcg only contains approximately 5.4 mg of budesonide. Chronic overdosage may result in signs/symptoms of hypercorticism (see WARNINGS and PRECAUTIONS).

DOSAGE AND ADMINISTRATION

The recommended starting dose for adults and children 6 years of age and older is 64 mcg per day administered as one spray per nostril of RHINOCORT AQUA Nasal Spray 32 mcg once daily. The maximum recommended dose for adults (12 years of age and older) is 256 mcg per day administered as four sprays per nostril once daily of RHINOCORT AQUA Nasal Spray 32 mcg and the maximum recommended dose for pediatric patients (<12 years of age) is 128 mcg per day administered as two sprays per nostril once daily of RHINOCORT AQUA Nasal Spray 32 mcg (see HOW SUPPLIED).

Prior to initial use, the container must be shaken gently and the pump must be primed by actuating eight times. If used daily, the pump does not need to be reprimed. If not used for two consecutive days, reprime with one spray or until a fine spray appears. If not used for more than 14 days, rinse the applicator and reprime with two sprays or until a fine spray appears.

Individualization of Dosage

It is always desirable to titrate an individual patient to the minimum effective dose to reduce the possibility of side effects. In adults and children 6 years of age and older, the recommended starting dose is 64 mcg daily administered as one spray per nostril of RHINOCORT AQUA Nasal Spray 32 mcg, once daily. Some patients who do not achieve symptom control at the recommended starting dose may benefit from an increased dose. The maximum daily dose is 256 mcg for adults and 128 mcg for pediatric patients (<12 years of age). When the maximum benefit has been achieved and symptoms have been controlled, reducing the dose may be effective in maintaining control of the allergic rhinitis symptoms in patients who were initially controlled on higher doses.

An improvement in nasal symptoms may be noted in patients within 10 hours of first using RHINOCORT AQUA Nasal Spray. This time to onset is supported by an environmental exposure unit study in seasonal allergic rhinitis patients which demonstrated that RHINOCORT AQUA Nasal Spray led to a statistically significant improvement in nasal symptoms compared to placebo by 10 hours. Further support comes from a clinical study of patients with perennial allergic rhinitis which demonstrated a statistically significant improvement in nasal symptoms for both RHINOCORT AQUA Nasal Spray and for the active comparator (mometasone furoate) compared to placebo by 8 hours. Onset was also assessed in this study with peak nasal inspiratory flow rate and this endpoint failed to show efficacy for either active treatment. Although statistically significant improvements in nasal symptoms compared to placebo were noted within 8-10 hours in these studies, about one half to two thirds of the ultimate clinical improvement with RHINOCORT AQUA Nasal Spray occurs over the first 1-2 days, and maximum benefit may not be achieved until approximately 2 weeks after initiation of treatment. Initial assessment for response should be made during this time frame and periodically until the patient's symptoms are stabilized.

Directions for Use

Illustrated *Patient's Instructions for Use* accompany each package of RHINOCORT AQUA Nasal Spray 32 mcg.

HOW SUPPLIED

RHINOCORT AQUA Nasal Spray 32 mcg is available in an amber glass bottle with a metered-dose pump spray and a green protection cap. RHINOCORT AQUA Nasal Spray 32 mcg provides 120 metered sprays after initial priming; net fill weight 8.6 g. The RHINOCORT AQUA Nasal Spray 32 mcg bottle has been filled with an excess to accommodate the priming activity. The bottle should be discarded after 120 sprays following initial priming, since the amount of budesonide delivered per spray thereafter may be substantially less than the labeled dose. Each spray delivers 32 mcg of budesonide to the patient.

NDC 0186-1070-08
RHINOCORT AQUA Nasal Spray
32 mcg, 120 metered sprays; net fill weight 8.6 g

RHINOCORT AQUA Nasal Spray should be stored at controlled room temperature, 20 to 25°C (68 to 77°F) with the valve up. Do not freeze. Protect from light. **Shake gently before use.** Do not spray in eyes.

REFERENCES

1 Kallen B, Rydhstroem H, Aberg A. Congenital malformations after the use of inhaled budesonide in early pregnancy. *Obstet Gynecol* 1999;93:392-395.

2 Ericson A, Kallen B. Use of drugs during pregnancy: unique Swedish registration method that can be improved. Swedish Medical Products Agency 1999;1:8-11.

3 Norjavaara E, Gerhardsson de Verdier M. Normal pregnancy outcomes in a population-based study including 2968 pregnant women exposed to budesonide. *J Allergy Clin Immunol* 2003;111:736-742.

Distributed by:
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Rev. 01/05

AstraZeneca

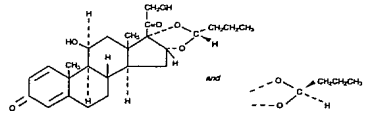
Pulmicort 200 mcg Turbuhaler®
(budesonide inhalation powder)

33020-00

For Oral Inhalation Only.
Rx only

DESCRIPTION

Budesonide, the active component of PULMICORT TURBUHALER 200 mcg, is a corticosteroid designated chemically as (RS)-11β,16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is $C_{25}H_{34}O_6$ and its molecular weight is 430.5. Its structural formula is:



Budesonide is a white to off-white, tasteless, odorless powder that is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform. Its partition coefficient between octanol and water at pH 7.4 is 1.6×10^3.

PULMICORT TURBUHALER is an inhalation-driven multi-dose dry powder inhaler that contains only micronized budesonide. Each actuation of PULMICORT TURBUHALER provides 200 mcg budesonide per metered dose, which delivers approximately 160 mcg budesonide from the mouthpiece (based on *in vitro* testing at 60 L/min for 2 sec).

In vitro testing has shown that the dose delivery for PULMICORT TURBUHALER is substantially dependent on airflow through the device. Patient factors such as inspiratory flow rates will also affect the dose delivered to the lungs of patients in actual use (see *Patient's Instructions for Use*). In adult patients with asthma (mean FEV_1 2.9 L [0.8–5.1 L]) mean peak inspiratory flow (PIF) through PULMICORT TURBUHALER was 78 (40–111) L/min. Similar results (mean PIF 82 [43–125] L/min) were obtained in asthmatic children (6 to 15 years, mean FEV_1 2.1 L [0.9–5.4 L]). Patients should be carefully instructed on the use of this drug product to assure optimal dose delivery.

CLINICAL PHARMACOLOGY

Mechanism of Action

Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay.

The activity of PULMICORT TURBUHALER is due to the parent drug, budesonide. In glucocorticoid receptor affinity studies, the 22R form was two times as active as the 22S epimer. *In vitro* studies indicated that the two forms of budesonide do not interconvert.

The precise mechanism of corticosteroid actions on inflammation in asthma is not known. Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (eg, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (eg, histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic and non-allergic-mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Studies in asthmatic patients have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects over a wide range of doses from PULMICORT TURBUHALER. This is explained by a combination of a relatively high local anti-inflammatory effect, extensive first pass hepatic degradation of orally absorbed drug (85-95%), and the low potency of formed metabolites (see below).

Pharmacokinetics

Absorption: After oral administration of budesonide, peak plasma concentration was achieved in about 1 to 2 hours and the absolute systemic availability was 6-13%. In contrast, most of budesonide delivered to the lungs is systemically absorbed. In healthy subjects, 34% of the metered dose was deposited in the lungs (as assessed by plasma concentration method) with an absolute systemic availability of 39% of the metered dose. Pharmacokinetics of budesonide do not differ significantly in healthy volunteers and asthmatic patients. Peak plasma concentrations of budesonide occurred within 30 minutes of inhalation from PULMICORT TURBUHALER.

In asthmatic patients, budesonide showed a linear increase in AUC and C_{max} with increasing dose after both a single dose and repeated dosing from PULMICORT TURBUHALER.

Distribution: The volume of distribution of budesonide was approximately 3 L/kg. It was 85-90% bound to plasma proteins. Protein binding was constant over the concentration range (1–100 nmol/L) achieved with, and exceeding, recommended doses of PULMICORT TURBUHALER. Budesonide showed little or no binding to corticosteroid binding globulin. Budesonide rapidly equilibrated with red blood cells in a concentration independent manner with a blood/plasma ratio of about 0.8.

Metabolism: *In vitro* studies with human liver homogenates have shown that budesonide is rapidly and extensively metabolized. Two major metabolites formed via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4) catalyzed biotransformation have been isolated and identified as 16α-hydroxyprednisolone and 6β-hydroxybudesonide. The corticosteroid activity of each of these two metabolites is less than 1% of that of the parent compound. No

qualitative differences between the *in vitro* and *in vivo* metabolic patterns have been detected. Negligible metabolic inactivation was observed in human lung and serum preparations.

Excretion/Elimination: The 22R form of budesonide was preferentially cleared by the liver with systemic clearance of 1.4 L/min vs. 1.0 L/min for the 22S form. The terminal half-life, 2 to 3 hours, was the same for both epimers and was independent of dose. Budesonide was excreted in urine and feces in the form of metabolites. Approximately 60% of an intravenous radiolabelled dose was recovered in the urine. No unchanged budesonide was detected in the urine.

Special Populations: No pharmacokinetic differences have been identified due to race, gender or advanced age.

Pediatric: Following intravenous dosing in pediatric patients age 10–14 years, plasma half-life was shorter than in adults (1.5 hours vs. 2.0 hours in adults). In the same population following inhalation of budesonide via a pressurized metered-dose inhaler, absolute systemic availability was similar to that in adults.

Hepatic Insufficiency: Reduced liver function may affect the elimination of corticosteroids. The pharmacokinetics of budesonide were affected by compromised liver function as evidenced by a doubled systemic availability after oral ingestion. The intravenous pharmacokinetics of budesonide were, however, similar in cirrhotic patients and in healthy subjects.

Drug-Drug Interactions: Ketoconazole, a potent inhibitor of cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4), the main metabolic enzyme for corticosteroids, increased plasma levels of orally ingested budesonide. At recommended doses, cimetidine had a slight but clinically insignificant effect on the pharmacokinetics of oral budesonide.

Pharmacodynamics

To confirm that systemic absorption is not a significant factor in the clinical efficacy of inhaled budesonide, a clinical study in patients with asthma was performed comparing 400 mcg budesonide administered via a pressurized metered-dose inhaler with a tube spacer to 1400 mcg of oral budesonide and placebo. The study demonstrated the efficacy of inhaled budesonide but not orally ingested budesonide despite comparable systemic levels. Thus, the therapeutic effect of conventional doses of orally inhaled budesonide are largely explained by its direct action on the respiratory tract.

Generally, PULMICORT TURBUHALER has a relatively rapid onset of action for an inhaled corticosteroid. Improvement in asthma control following inhalation of PULMICORT TURBUHALER can occur within 24 hours of beginning treatment although maximum benefit may not be achieved for 1 to 2 weeks, or longer.

PULMICORT TURBUHALER has been shown to decrease airway reactivity to various challenge models, including histamine, methacholine, sodium metabisulfite, and adenosine monophosphate in patients with hyperreactive airways. The clinical relevance of these models is not certain.

Pretreatment with PULMICORT TURBUHALER 1600 mcg daily (800 mcg twice daily) for 2 weeks reduced the acute (early-phase reaction) and delayed (late-phase reaction) decrease in FEV_1 following inhaled allergen challenge.

The effects of PULMICORT TURBUHALER on the hypothalamic-pituitary-adrenal (HPA) axis were studied in 905 adults and 404 pediatric patients with asthma. For most patients, the ability to increase cortisol production in response to stress, as assessed by cosyntropin (ACTH) stimulation test, remained intact with PULMICORT TURBUHALER treatment at recommended doses. For adult patients treated with 100, 200, 400, or 800 mcg twice daily for 12 weeks, 4%, 2%, 6%, and 13% respectively, had an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL assessed by liquid chromatography following short-cosyntropin test) as compared with 8% of patients treated with placebo. Similar results were obtained in pediatric patients. In another study in adults, doses of 400, 800 and 1600 mcg budesonide twice daily via PULMICORT TURBUHALER for 6 weeks were examined; 1600 mcg twice daily (twice the maximum recommended dose) resulted in a 27% reduction in stimulated cortisol (6-hour ACTH infusion) while 10 mg prednisone resulted in a 35% reduction. In this study, no patient on PULMICORT TURBUHALER at doses of 400 and 800 mcg twice daily met the criterion for an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL assessed by liquid chromatography) following ACTH infusion. An open-label, long-term follow-up of 1133 patients for up to 52 weeks confirmed the minimal effect on the HPA axis (both basal and stimulated plasma cortisol) of PULMICORT TURBUHALER when administered at recommended doses. In patients who had previously been oral steroid-dependent, use of PULMICORT TURBUHALER in recommended doses was associated with higher stimulated cortisol response compared with baseline following 1 year of therapy.

The administration of budesonide via PULMICORT TURBUHALER in doses up to 800 mcg/day (mean daily dose 445 mcg/day) or via a pressurized metered-dose inhaler in doses up to 1200 mcg/day (mean daily dose 620 mcg/day) to 216 pediatric patients (age 3 to 11 years) for 2 to 6 years had no significant effect on statural growth compared with non-corticosteroid therapy in 62 matched control patients. However, the long-term effect of PULMICORT TURBUHALER on growth is not fully known.

CLINICAL TRIALS

The therapeutic efficacy of PULMICORT TURBUHALER has been evaluated in controlled clinical trials involving more than 1300 patients (6 years and older) with asthma of varying disease duration (<1 year to >20 years) and severity.

Double-blind, parallel, placebo-controlled clinical trials of 12 weeks duration and longer have shown that, compared with placebo, PULMICORT TURBUHALER significantly improved lung function (measured by PEF and FEV_1), significantly decreased morning and evening symptoms of asthma, and significantly reduced the need for as-needed inhaled β_2-agonist use at doses of 400 mcg to 1600 mcg per day (200 mcg to 800 mcg twice daily) in adults and 400 mcg to 800 mcg per day (200 mcg to 400 mcg twice daily) in pediatric patients 6 years of age and older.

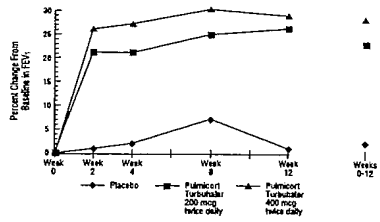
Improved lung function (morning PEF) was observed within 24 hours of initiating treatment in both adult and pediatric patients 6 years of age and older, although maximum benefit was not achieved for 1 to 2 weeks, or longer, after starting treatment. Improved lung function was maintained throughout the 12 weeks of the double-blind portion of the trials.

PULMICORT TURBUHALER® (budesonide inhalation powder) For Oral Inhalation Only.

Patients Not Receiving Corticosteroid Therapy

In a 12-week clinical trial in 273 patients with mild to moderate asthma (mean baseline FEV_1 2.27 L) who were not well controlled by bronchodilators alone, PULMICORT TURBUHALER was evaluated at doses of 200 mcg twice daily and 400 mcg twice daily versus placebo. The FEV_1 results from this trial are shown in the figure below. Pulmonary function improved significantly on both doses of PULMICORT TURBUHALER compared with placebo.

A 12-Week Trial in Patients Not on Corticosteroid Therapy Prior to Study Entry

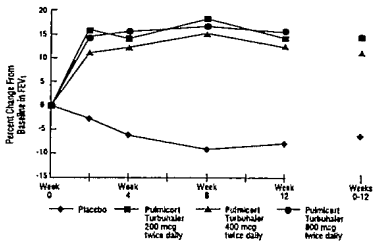


In a 12-month controlled trial in 75 patients not previously receiving corticosteroids, PULMICORT TURBUHALER at 200 mcg twice daily resulted in improved lung function (measured by PEF) and reduced bronchial hyperreactivity compared with placebo.

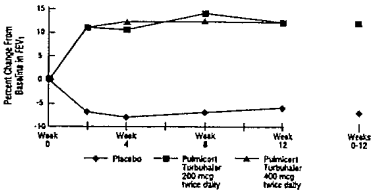
Patients Previously Maintained on Inhaled Corticosteroids

The safety and efficacy of PULMICORT TURBUHALER was also evaluated in adult and pediatric patients (age 6 to 18 years) previously maintained on inhaled corticosteroids (adults: N=473, mean baseline FEV_1 2.04 L, baseline doses of beclomethasone dipropionate 126-1008 mcg/day; pediatrics: N=404, mean baseline FEV_1 2.09 L, baseline doses of beclomethasone dipropionate 126-672 mcg/day or triamcinolone acetonide 300-1800 mcg/day). The FEV_1 results of these two trials, both 12 weeks in duration, are presented in the following figures. Pulmonary function improved significantly with all doses of PULMICORT TURBUHALER compared with placebo in both trials.

Adult Patients Previously Maintained on Inhaled Corticosteroids



Pediatric Patients Age 6 to 18 Years Previously Maintained on Inhaled Corticosteroids



Patients Receiving PULMICORT TURBUHALER Once Daily

The efficacy and safety of once-daily administration of PULMICORT TURBUHALER 200 mcg and 400 mcg and placebo were also evaluated in 309 adult asthmatic patients (mean baseline FEV_1 2.7 L) in an 18-week study. Compared with placebo, patients receiving Pulmicort 200 or 400 mcg once daily showed significantly better asthma stability as assessed by PEF and FEV_1 over an initial 6-week treatment period, which was maintained with a 200 mcg daily dose over the subsequent 12 weeks. Although the study population included both patients previously treated with inhaled corticosteroids, as well as patients not previously receiving corticosteroid therapy, the results showed that once-daily dosing was most clearly effective for those patients previously maintained on orally inhaled corticosteroids (see DOSAGE AND ADMINISTRATION).

Patients Previously Maintained on Oral Corticosteroids

In a clinical trial in 159 severe asthmatic patients requiring chronic oral prednisone therapy (mean baseline prednisone dose 19.3 mg/day) PULMICORT TURBUHALER at doses of 400 mcg twice daily and 800 mcg twice daily was compared to placebo over a 20-week period. Approximately two-thirds (68% on 400 mcg twice daily and 64% on 800 mcg twice daily) of PULMICORT TURBUHALER-treated patients were able to achieve sustained (at least 2 weeks) oral corticosteroid cessation (compared with 8% of placebo-treated patients) and improved asthma control. The average oral corticosteroid dose was reduced by 83% on 400 mcg twice daily and 79% on 800 mcg twice daily for PULMICORT TURBUHALER-treated patients vs. 27% for placebo. Additionally, 58 out of 64 patients (91%) who completely eliminated oral corticosteroids during the double-blind phase of the trial remained off oral corticosteroids for an additional 12 months while receiving PULMICORT TURBUHALER.

INDICATIONS AND USAGE

PULMICORT TURBUHALER is indicated for the maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients six years of age or older. It is also indicated for patients requiring oral corticosteroid therapy for asthma. Many of those patients may be able to reduce or eliminate their requirement for oral corticosteroids over time.

PULMICORT TURBUHALER is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

PULMICORT TURBUHALER is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to budesonide contraindicates the use of PULMICORT TURBUHALER.

WARNINGS

Particular care is needed for patients who are transferred from systemically active corticosteroids to PULMICORT TURBUHALER because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although PULMICORT TURBUHALER may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a medical identification card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to PULMICORT TURBUHALER. Lung function (FEV_1 or AM PEF), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to PULMICORT TURBUHALER may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy, eg, rhinitis, conjunctivitis, arthritis, eosinophilic conditions, and eczema (see DOSAGE AND ADMINISTRATION).

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible pediatric patients or adults on immunosuppressant doses of corticosteroids. In pediatric or adult patients who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered.

PULMICORT TURBUHALER is not a bronchodilator and is not indicated for rapid relief of bronchospasm or other acute episodes of asthma.

As with other inhaled asthma medications, bronchospasm, with an immediate increase in wheezing, may occur after dosing. If bronchospasm occurs following dosing with PULMICORT TURBUHALER, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with PULMICORT TURBUHALER should be discontinued and alternate therapy instituted.

Patients should be instructed to contact their physician immediately when episodes of asthma not responsive to their usual doses of bronchodilators occur during treatment with PULMICORT TURBUHALER. During such episodes, patients may require therapy with oral corticosteroids.

PRECAUTIONS

General

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, eg, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function (see DOSAGE AND ADMINISTRATION).

In responsive patients, PULMICORT TURBUHALER may permit control of asthma symptoms with less suppression of HPA-axis function than therapeutically equivalent oral doses of prednisone. Since budesonide is absorbed into the circulation and can be systemically active, the beneficial effects of PULMICORT TURBUHALER in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing PULMICORT TURBUHALER.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with PULMICORT TURBUHALER should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism, reduced bone mineral density, and adrenal suppression may appear in a small number of patients, particularly at higher doses. If such changes occur, PULMICORT TURBUHALER should be reduced slowly, consistent with accepted procedures for management of asthma symptoms and for tapering of systemic steroids.

Orally inhaled corticosteroids, including budesonide, may cause a reduction in growth velocity when administered to pediatric patients. A reduction in growth velocity may occur as a result of inadequate control of asthma or from use of corticosteroids for treatment. The potential effects of prolonged treatment on growth velocity should be weighed against the clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including PULMICORT TURBUHALER, each patient should be titrated to his/her lowest effective dose (see PRECAUTIONS, Pediatric Use).

Although patients in clinical trials have received PULMICORT TURBUHALER on a continuous basis for periods of 1 to 2 years, the long-term local and systemic effects of PULMICORT TURBUHALER in human subjects are not completely known. In particular, the effects resulting from chronic use of PULMICORT TURBUHALER on developmental or immunological processes in the mouth, pharynx, trachea, and lung are unknown.

In clinical trials with PULMICORT TURBUHALER, localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. These infections may require treatment with appropriate antifungal therapy and/or discontinuance of treatment with PULMICORT TURBUHALER.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract, untreated systemic fungal, bacterial, viral or parasitic infections, or ocular herpes simplex.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids.

Information for Patients

Patients being treated with PULMICORT TURBUHALER should receive the following information and instructions. This information is intended to aid the patient in the safe and effective use of the medication. It is not a disclosure of all possible adverse or intended effects. For proper use of PULMICORT TURBUHALER and to attain maximum improvement, the patient should read and follow the accompanying *Patient's Instructions for Use* carefully.

- Patients should use PULMICORT TURBUHALER at regular intervals as directed since its effectiveness depends on regular use. The patient should not alter the prescribed dosage unless advised to do so by the physician.
- Patients should be advised that PULMICORT TURBUHALER is not a bronchodilator and is not intended to treat acute or life-threatening episodes of asthma.
- Patients should be advised that the effectiveness of PULMICORT TURBUHALER depends on proper use of the device and inhalation-administering technique:
  1. PULMICORT TURBUHALER must be in the upright position (mouthpiece on top) during loading in order to provide the correct dose.
  2. PULMICORT TURBUHALER must be primed when the unit is used for the very first time. To prime the unit, it must be held in an upright position and the brown grip turned fully to the right, then turned fully to the left until it clicks. Repeat.
  3. To load the first dose, the grip must be turned fully to the right and fully to the left until it clicks.
  4. After the first dose, it is not necessary to prime the unit. However, it must be loaded in the upright position immediately prior to use as described above.
  5. Patients should be advised not to shake the inhaler.
- Patients should place the mouthpiece between the lips and inhale forcefully and deeply. The powder is then delivered to the lungs.
- Patients should not exhale through PULMICORT TURBUHALER.
- Due to the small volume of powder, the patient may not taste or sense the presence of any medication entering the lungs when inhaling from the TURBUHALER inhaler. This lack of sensation does not indicate that the patient is not receiving benefit from PULMICORT TURBUHALER.
- Patients should be advised that rinsing the mouth with water without swallowing after each dosing may decrease the risk of the development of oral candidiasis.
- Patients should be instructed that they will receive a new PULMICORT TURBUHALER unit each time they refill their prescription. Patients should be advised to discard the whole device after the labelled number of inhalations has been used. When there are 20 doses remaining in PULMICORT TURBUHALER, a red mark will appear in the indicator window.
- PULMICORT TURBUHALER should not be used with a spacer.
- The mouthpiece should not be bitten or chewed.
- The cover should be replaced securely after each opening.
- Patients should keep PULMICORT TURBUHALER clean and dry at all times.
- Patients should be advised that improvement in asthma control following inhalation of PULMICORT TURBUHALER can occur within 24 hours of beginning treatment although maximum benefit may not be achieved for 1 to 2 weeks, or longer. If symptoms do not improve in that time frame, or if the condition worsens, the patient should be instructed not to increase the dosage, but to contact the physician.
- Patients whose systemic corticosteroids have been reduced or withdrawn should be instructed to carry a warning card indicating that they may need supplemental systemic corticosteroids during periods of stress or an asthma attack that does not respond to bronchodilators.
- Patients should be advised not to stop the use of PULMICORT TURBUHALER abruptly.
- Patients should be warned to avoid exposure to chicken pox or measles and if they are exposed, to consult their physicians without delay.
- Long-term use of inhaled corticosteroids, including budesonide, may increase the risk of some eye problems (cataracts or glaucoma). Regular eye examinations should be considered.
- Women considering the use of PULMICORT TURBUHALER should consult with their physician if they are pregnant or intend to become pregnant, or if they are breast-feeding a baby.
- Patients considering use of PULMICORT TURBUHALER should consult with their physician if they are allergic to budesonide or any other orally inhaled corticosteroid.
- Patients should inform their physician of other medications they are taking as PULMICORT TURBUHALER may not be suitable in some circumstances and the physician may wish to use a different medicine.

Drug Interactions

In clinical studies, concurrent administration of budesonide and other drugs commonly used in the treatment of asthma has not resulted in an increased frequency of adverse events. The main route of metabolism of budesonide, as well as other corticosteroids, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a potent inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of other known inhibitors of CYP3A4 (eg, itraconazole, clarithromycin, erythromycin, etc.) may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Care should be exercised when budesonide is coadministered with long-term ketoconazole and other known CYP3A4 inhibitors.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies were conducted in rats and mice using oral administration to evaluate the carcinogenic potential of budesonide.

In a 104-week oral study in Sprague-Dawley rats, a statistically significant increase in the incidence of gliomas was observed in male rats receiving an oral dose of 50 mcg/kg/day (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m^2 basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m^2 basis). In two additional two-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m^2 basis). However, in the male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m^2 basis). The concurrent reference corticosteroids (prednisone and triamcinolone acetonide) in these two studies showed similar findings.

There was no evidence of a carcinogenic effect when budesonide was administered orally for 91 weeks to mice at doses up to 200 mcg/kg/day (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m^2 basis).

Budesonide was not mutagenic or clastogenic in six different test systems: Ames *Salmonella*/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in *Drosophila melanogaster*, and DNA repair analysis in rat hepatocyte culture.

In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

At 20 mcg/kg/day (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis), decreases in maternal body weight gain, prenatal viability, and viability of the young at birth and during lactation were observed. No such effects were noted at 5 mcg/kg (less than the maximum recommended human daily inhalation dose in adults on a mcg/m^2 basis).

Pregnancy: Teratogenic Effects

Pregnancy Category B: As with other glucocorticoids, budesonide produced fetal loss, decreased pup weight, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg/day in rabbits (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis) and 500 mcg/kg/day in rats (approximately 3 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

No teratogenic or embryocidal effects were observed in rats when budesonide was administered by inhalation at doses up to 250 mcg/kg/day (equivalent to the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Experience with oral corticosteroids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

Studies of pregnant women, however, have not shown that PULMICORT TURBUHALER increases the risk of abnormalities when administered during pregnancy. The results from a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995–1997 (i.e., Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry) indicate no increased risk for congenital malformations from the use of inhaled budesonide during early pregnancy. Congenital malformations were studied in 2,014 infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 10–12 weeks after the last menstrual period), the period when most major organ malformations occur. The rate of recorded congenital malformations was similar compared to the general population rate (3.8% vs. 3.5%, respectively). In addition, after exposure to inhaled budesonide, the number of infants born with orofacial clefts was similar to the expected number in the normal population (4 children vs. 3.3, respectively).

These same data were utilized in a second study bringing the total to 2,534 infants whose mothers were exposed to inhaled budesonide. In this study, the rate of congenital malformations among infants whose mothers were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%).

Despite the animal findings, it would appear that the possibility of fetal harm is remote if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, PULMICORT TURBUHALER should be used during pregnancy only if clearly needed.

Nonteratogenic Effects

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers

Corticosteroids are secreted in human milk. Because of the potential for adverse reactions in nursing infants from any corticosteroid, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. Actual data for budesonide are lacking.

Pediatric Use

Safety and effectiveness of PULMICORT TURBUHALER in pediatric patients below 6 years of age have not been established.

In pediatric asthma patients the frequency of adverse events observed with PULMICORT TURBUHALER was similar between the 6- to 12-year age group (N=172) compared with the 13- to 17-year age group (N=124).

Controlled clinical studies have shown that orally inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids including the impact on final adult height are unknown. The potential for "catch up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

In a study of asthmatic children 5-12 years of age, those treated with PULMICORT TURBUHALER 200 mcg twice daily (n=311) had a 1.1-centimeter reduction in growth compared with those receiving placebo (n=418) at the end of one year; the difference between these two treatment groups did not increase further over three years of additional treatment. By the end of four years, children treated with PULMICORT TURBUHALER and children treated with placebo had similar growth velocities. Conclusions drawn from this study may be confounded by the unequal use of corticosteroids in the treatment groups and inclusion of data from patients attaining puberty during the course of the study.

The growth of pediatric patients receiving orally inhaled corticosteroids, including PULMICORT TURBUHALER, should be monitored routinely (eg, via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks and benefits associated with alternative therapies. To minimize the systemic effects of inhaled corticosteroids, including PULMICORT TURBUHALER, each patient should be titrated to his/her lowest effective dose.

Geriatric Use

One hundred patients 65 years or older were included in the US and non-US controlled clinical trials of PULMICORT TURBUHALER. There were no differences in the safety and efficacy of the drug compared to those seen in younger patients.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The following adverse reactions were reported in patients treated with PULMICORT TURBUHALER.

The incidence of common adverse events is based upon double-blind, placebo-controlled US clinical trials in which 1116 adult and pediatric patients age 6-70 years (472 females and 644 males) were treated with PULMICORT TURBUHALER (200 to 800 mcg twice daily for 12 to 20 weeks) or placebo.

The following table shows the incidence of adverse events in patients previously receiving bronchodilators and/or inhaled corticosteroids in US controlled clinical trials. This population included 232 male and 62 female pediatric patients (age 6 to 17 years) and 332 male and 331 female adult patients (age 18 years and greater).

Adverse Events with ≥3% Incidence reported by Patients on PULMICORT TURBUHALER

		PULMICORT TURBUHALER		
Adverse Event	Placebo N=284 %	200 mcg twice daily N=286 %	400 mcg twice daily N=289 %	800 mcg twice daily N=98 %
Respiratory System				
Respiratory infection	17	20	24	19
Pharyngitis	9	10	9	5
Sinusitis	7	11	7	2
Voice alteration	0	1	2	6
Body As A Whole				
Headache	7	14	13	14
Flu syndrome	6	6	6	14
Pain	2	5	5	5
Back pain	1	2	3	6
Fever	2	2	4	0
Digestive System				
Oral candidiasis	2	2	4	4
Dyspepsia	2	1	2	4
Gastroenteritis	1	1	2	3
Nausea	2	2	1	3
Average Duration of Exposure (days)	59	79	80	80

PULMICORT TURBUHALER® (budesonide inhalation powder) For Oral Inhalation Only.

The table above includes all events (whether considered drug-related or non-drug-related by the investigators) that occurred at a rate of ≥3% in any one PULMICORT TURBUHALER group and were more common than in the placebo group. In considering these data, the increased average duration of exposure for PULMICORT TURBUHALER patients should be taken into account.

The following other adverse events occurred in these clinical trials using PULMICORT TURBUHALER with an incidence of 1 to 3% and were more common on PULMICORT TURBUHALER than on placebo.

Body As A Whole: neck pain
Cardiovascular: syncope
Digestive: abdominal pain, dry mouth, vomiting
Metabolic and Nutritional: weight gain
Musculoskeletal: fracture, myalgia
Nervous: hypertonia, migraine
Platelet, Bleeding and Clotting: ecchymosis
Psychiatric: insomnia
Resistance Mechanisms: infection
Special Senses: taste perversion

In a 20-week trial in adult asthmatics who previously required oral corticosteroids, the effects of PULMICORT TURBUHALER 400 mcg twice daily (N=53) and 800 mcg twice daily (N=53) were compared with placebo (N=53) on the frequency of reported adverse events. Adverse events, whether considered drug-related or non-drug-related by the investigators, reported in more than five patients in the PULMICORT TURBUHALER group and which occurred more frequently with PULMICORT TURBUHALER than placebo are shown below (% PULMICORT TURBUHALER and % placebo). In considering these data, the increased average duration of exposure for PULMICORT TURBUHALER patients (78 days for PULMICORT TURBUHALER vs. 41 days for placebo) should be taken into account.

Body As A Whole:	asthenia (9% and 2%) headache (12% and 2%) pain (10% and 2%)
Digestive:	dyspepsia (8% and 0%) nausea (6% and 0%) oral candidiasis (10% and 0%)
Musculoskeletal:	arthralgia (6% and 0%)
Respiratory:	cough increased (6% and 2%) respiratory infection (32% and 13%) rhinitis (6% and 2%) sinusitis (16% and 11%)

Patient Receiving PULMICORT TURBUHALER Once Daily

The adverse event profile of once-daily administration of PULMICORT TURBUHALER 200 mcg and 400 mcg, and placebo, was evaluated in 309 adult asthmatic patients in an 18-week study. The study population included both patients previously treated with inhaled corticosteroids, and patients not previously receiving corticosteroid therapy. There was no clinically relevant difference in the pattern of adverse events following once-daily administration of PULMICORT TURBUHALER when compared with twice-daily dosing.

Pediatric Studies: In a 12-week placebo-controlled trial in 404 pediatric patients 6 to 18 years of age previously maintained on inhaled corticosteroids, the frequency of adverse events for each age category (6 to 12 years, 13 to 18 years) was comparable for PULMICORT TURBUHALER (at 100, 200 and 400 mcg twice daily) and placebo. There were no clinically relevant differences in the pattern or severity of adverse events in children compared with those reported in adults.

Adverse Event Reports From Other Sources: Rare adverse events reported in the published literature or from worldwide marketing experience with any formulation of inhaled budesonide include: immediate and delayed hypersensitivity reactions including rash, contact dermatitis, urticaria, angioedema and bronchospasm; symptoms of hypocorticism and hypercorticism; glaucoma, cataracts; psychiatric symptoms including depression, aggressive reactions, irritability, anxiety and psychosis.

OVERDOSAGE

The potential for acute toxic effects following overdose of PULMICORT TURBUHALER is low. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur (see PRECAUTIONS). PULMICORT TURBUHALER at twice the highest recommended dose (3200 mcg daily) administered for 6 weeks caused a significant reduction (27%) in the plasma cortisol response to a 6-hour infusion of ACTH compared with placebo (+1%). The corresponding effect of 10 mg prednisone daily was a 35% reduction in the plasma cortisol response to ACTH.

The minimal inhalation lethal dose in mice was 100 mg/kg (approximately 320 times the maximum recommended daily inhalation dose in adults and approximately 380 times the maximum recommended daily inhalation dose in children on a mcg/m^2 basis). There were no deaths following the administration of an inhalation dose of 68 mg/kg in rats (approximately 430 times the maximum recommended daily inhalation dose in adults and approximately 510 times the maximum recommended daily inhalation dose in children on a mcg/m^2 basis). The minimal oral lethal dose was 200 mg/kg in mice (approximately 630 times the maximum recommended daily inhalation dose in adults and approximately 750 times the maximum recommended daily inhalation dose in children on a mcg/m^2 basis) and less than 100 mg/kg in rats (approximately 630 times the maximum recommended daily inhalation dose in adults and approximately 750 times the maximum recommended daily inhalation dose in children based on a mcg/m^2 basis).

Post-marketing experience showed that patients experiencing acute overdose of inhaled budesonide commonly remained asymptomatic. The use of excessive doses (up to 6400 mcg daily) for prolonged periods showed systemic corticosteroid effects such as hypercorticism.

DOSAGE AND ADMINISTRATION

PULMICORT TURBUHALER should be administered by the orally inhaled route in asthmatic patients age 6 years and older. Individual patients will experience a variable onset and degree of symptom relief. Generally, PULMICORT TURBUHALER has a relatively rapid onset of action for an inhaled corticosteroid. Improvement in asthma control following inhaled administration of PULMICORT TURBUHALER can occur within 24 hours of initiation of treatment, although maximum benefit may not be achieved for 1 to 2 weeks, or longer. The safety and efficacy of PULMICORT TURBUHALER when administered in excess of recommended doses have not been established.

PULMICORT TURBUHALER® (budesonide inhalation powder) For Oral Inhalation Only.

The recommended starting dose and the highest recommended dose of PULMICORT TURBUHALER, based on prior asthma therapy, are listed in the following table.

	Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Adults:	Bronchodilators alone	200 to 400 mcg twice daily	400 mcg twice daily
	Inhaled Corticosteroids*	200 to 400 mcg twice daily	800 mcg twice daily
	Oral Corticosteroids	400 to 800 mcg twice daily	800 mcg twice daily
Children:	Bronchodilators alone	200 mcg twice daily	400 mcg twice daily
	Inhaled Corticosteroids*	200 mcg twice daily	400 mcg twice daily
	Oral Corticosteroids	The highest recommended dose in children is 400 mcg twice daily	

*In patients with mild to moderate asthma who are well controlled on inhaled corticosteroids, dosing with PULMICORT TURBUHALER 200 mcg or 400 mcg once daily may be considered. PULMICORT TURBUHALER can be administered once daily either in the morning or in the evening.

If the once-daily treatment with PULMICORT TURBUHALER does not provide adequate control of asthma symptoms, the total daily dose should be increased and/or administered as a divided dose.

Patients Maintained on Chronic Oral Corticosteroids

Initially, PULMICORT TURBUHALER should be used concurrently with the patient's usual maintenance dose of systemic corticosteroid. After approximately one week, gradual withdrawal of the systemic corticosteroid is started by reducing the daily or alternate daily dose. The next reduction is made after an interval of one or two weeks, depending on the response of the patient. Generally, these decrements should not exceed 2.5 mg of prednisone or its equivalent. A slow rate of withdrawal is strongly recommended. During reduction of oral corticosteroids, patients should be carefully monitored for asthma instability, including objective measures of airway function, and for adrenal insufficiency (see WARNINGS). During withdrawal, some patients may experience symptoms of systemic corticosteroid withdrawal, eg, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement in pulmonary function. Such patients should be encouraged to continue with PULMICORT TURBUHALER but should be monitored for objective signs of adrenal insufficiency. If evidence of adrenal insufficiency occurs, the systemic corticosteroid doses should be increased temporarily and thereafter withdrawal should continue more slowly. During periods of stress or a severe asthma attack, transfer patients may require supplementary treatment with systemic corticosteroids.

NOTE: In all patients it is desirable to titrate to the lowest effective dose once asthma stability is achieved.

Directions for Use: Illustrated *Patient's Instructions for Use* accompany each package of PULMICORT TURBUHALER.

Patients should be instructed to prime PULMICORT TURBUHALER prior to its initial use, and instructed to inhale deeply and forcefully each time the unit is used. Rinsing the mouth after inhalation is also recommended.

HOW SUPPLIED

PULMICORT TURBUHALER consists of a number of assembled plastic details, the main parts being the dosing mechanism, the storage unit for drug substance and the mouthpiece. The inhaler is protected by a white outer tubular cover screwed onto the inhaler. The body of the inhaler is white and the turning grip is brown. The following wording is printed on the grip in raised lettering, "Pulmicort™ 200 mcg". The TURBUHALER inhaler cannot be refilled and should be discarded when empty.

PULMICORT TURBUHALER is available as 200 mcg/dose, 200 doses (NDC 0186-0915-42) and has a target fill weight of 104 mg.

When there are 20 doses remaining in PULMICORT TURBUHALER, a red mark will appear in the indicator window. If the unit is used beyond the point at which the red mark appears at the bottom of the window, the correct amount of medication may not be obtained. The unit should be discarded.

Store with the cover tightened in a dry place at controlled room temperature 20–25°C (68–77°F) [see USP]. Keep out of the reach of children.

Manufactured for: AstraZeneca LP, Wilmington, DE 19850
By: AstraZeneca AB, Södertälje, Sweden

33020-00
Rev. 10/06 248931

AstraZeneca

PATIENT'S INSTRUCTIONS FOR USE

33021-00

Pulmicort 200 mcg Turbuhaler®

(budesonide inhalation powder)

For Oral Inhalation Only.

Please read this leaflet carefully before you start to take your medicine. It provides a summary of information on your medicine. Following these instructions helps to ensure that you are inhaling the medication correctly.
FOR FURTHER INFORMATION ASK YOUR DOCTOR OR PHARMACIST.

WHAT YOU SHOULD KNOW ABOUT PULMICORT TURBUHALER

Your doctor has prescribed PULMICORT TURBUHALER 200 mcg. It contains a medication called budesonide, which is a synthetic corticosteroid. Corticosteroids are natural substances found in the body that help fight inflammation. They are used to treat asthma because they reduce the swelling and irritation in the walls of the small air passages in the lungs and ease breathing problems. When inhaled regularly, corticosteroids also help to prevent attacks of asthma.

PULMICORT TURBUHALER treats the inflammation—the "quiet part" of asthma that you cannot hear, see, or feel. When inflammation is left untreated, your asthma symptoms and attacks can increase. PULMICORT TURBUHALER works to prevent and reduce your asthma symptoms and attacks.

IMPORTANT POINTS TO REMEMBER ABOUT PULMICORT TURBUHALER

1. MAKE SURE that this medicine is suitable for you (see "BEFORE USING YOUR PULMICORT TURBUHALER").
2. It is important that you inhale each dose as your doctor has advised.
3. Use your Turbuhaler as directed by your doctor. **DO NOT STOP TREATMENT OR REDUCE YOUR DOSE EVEN IF YOU FEEL BETTER,** unless told to do so by your doctor.
4. **DO NOT** inhale more doses or use your Turbuhaler more often than instructed by your doctor.
5. This medicine is **NOT** intended to provide rapid relief of your breathing difficulties during an asthma attack. It must be taken at regular intervals as recommended by your doctor, and not as an emergency measure.
6. Your doctor may prescribe additional medication (such as bronchodilators) for emergency relief if an acute asthma attack occurs. Please contact your doctor if:
   - an asthma attack does not respond to the additional medication,
   - you require more of the additional medication than usual.
7. If you also use another medicine by inhalation, you should consult your doctor for instructions on when to use it in relation to using your PULMICORT TURBUHALER.

BEFORE USING YOUR PULMICORT TURBUHALER

TELL YOUR DOCTOR BEFORE STARTING TO TAKE THIS MEDICINE IF YOU:

- are pregnant (or intending to become pregnant),
- are breast-feeding a baby,
- are allergic to budesonide or any other orally inhaled corticosteroid,
- have any infections,
- have or had tuberculosis,
- have osteoporosis,
- have recently been around anyone with chicken pox or measles,
- are planning to have surgery,
- have been taking an oral corticosteroid medicine like prednisone. You may have to follow specific instructions to avoid health risks associated with stopping the use of these types of medicines.

In some circumstances, this medicine may not be suitable and your doctor may wish to prescribe a different medicine. Make sure that your doctor knows what other medicines you are taking including prescription and non-prescription medicines, as well as any vitamins or dietary and herbal supplements.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF PULMICORT TURBUHALER?

As with all inhaled corticosteroids, you should be aware of the following side effects:

- **Increased wheezing right after taking PULMICORT TURBUHALER. Always have a short-acting bronchodilator medicine with you to treat sudden wheezing.** Short-acting bronchodilator medicines help to relax the muscles around the airways in your lungs. Wheezing happens when the muscles around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and cause death if not treated right away.
- **Immune system effects and a higher chance of infections.**
- **Eye problems including glaucoma and cataracts.** Eye examinations should be considered while using PULMICORT TURBUHALER.
- A child's growth should be checked regularly while taking PULMICORT TURBUHALER because of the potential for slowed growth.

Based on clinical trials, the most common side effects reported by patients using PULMICORT TURBUHALER are:

- respiratory infection
- headache
- flu symptoms
- sore throat
- sinusitis

These are not all of the possible side effects of PULMICORT TURBUHALER. For more information, ask your doctor, healthcare professional, or pharmacist.

USING YOUR PULMICORT TURBUHALER

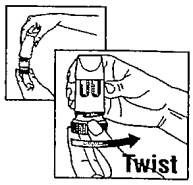
- Follow the instructions shown in the section "HOW TO USE YOUR PULMICORT TURBUHALER". If you have any problems, tell your doctor or pharmacist.
- It is important that you inhale each dose as directed by your doctor. The pharmacy label will usually tell you what dose to take and how often. If it doesn't, or you are not sure, ask your doctor or pharmacist.

DOSAGE

- Use as directed by your doctor.
- It is **VERY IMPORTANT** that you follow your doctor's instructions as to how many inhalations to take and how often to use your PULMICORT TURBUHALER.
- **DO NOT** inhale more doses or use your PULMICORT TURBUHALER more often than your doctor advises.
- It may take 1 to 2 weeks or longer before you feel maximum improvement, so **IT IS VERY IMPORTANT THAT YOU USE PULMICORT TURBUHALER REGULARLY. DO NOT STOP TREATMENT OR REDUCE YOUR DOSE EVEN IF YOU ARE FEELING BETTER,** unless told to do so by your doctor.
- If you miss a dose, just take your regularly scheduled next dose when it is due. **DO NOT DOUBLE** the dose.

HOW TO USE YOUR PULMICORT TURBUHALER

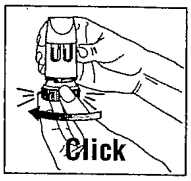
Read the complete instructions carefully and use only as directed.



PRIMING INSTRUCTIONS:

Before you use a new PULMICORT TURBUHALER for the first time, you should prime it. To do this, turn the cover and lift off. Hold PULMICORT TURBUHALER upright (with mouthpiece up), then twist the brown grip fully to the right and back again to the left. Repeat. Now you are ready to take your first dose (see instructions for "TAKING A DOSE"). **You do not have to prime it any other time after this, even if you put it aside for a prolonged period of time.**

TAKING A DOSE:



❶ LOADING A DOSE

- Twist the cover and lift off.
- In order to provide the correct dose, **PULMICORT TURBUHALER must be held in the upright position (mouthpiece up) whenever a dose of medication is being loaded.**
- Twist the brown grip fully to the right as far as it will go. Twist it back again fully to the left.
- You will hear a click.

❷ INHALING THE DOSE

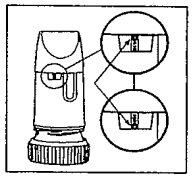
- When you are inhaling, PULMICORT TURBUHALER must be held in the upright (mouthpiece up) or horizontal position.
- Turn your head away from the inhaler and breathe out. **Do not shake the inhaler after loading it.**
- Place the mouthpiece between your lips and inhale deeply and forcefully. You may not taste or feel the medication.
- Do not chew or bite on the mouthpiece.
- Remove the inhaler from your mouth and exhale. Do not blow or exhale into the mouthpiece.
- If more than one dose is required, just repeat the steps above.
- **When you are finished, place the cover back on** the inhaler and twist shut. **Rinse your mouth with water. Do not swallow.**
- **Keep your PULMICORT TURBUHALER clean and dry at all times.**
- Do not use PULMICORT TURBUHALER if it has been damaged or if the mouthpiece has become detached.

STORING YOUR PULMICORT TURBUHALER

- After each use, place the white cover back on and twist it firmly into place.
- Keep PULMICORT TURBUHALER in a dry place at controlled room temperature, 68–77°F (20–25°C).
- Keep your PULMICORT TURBUHALER in a secure place out of the **reach of young children.**
- **DO NOT** use after the date shown on the body of your Turbuhaler.

HOW TO KNOW WHEN YOUR PULMICORT TURBUHALER IS EMPTY

The label on the box or cover will tell you how many doses are in your PULMICORT TURBUHALER.



Your PULMICORT TURBUHALER has a convenient dose indicator window just below the mouthpiece.

- **When a red mark appears at the top of the window, there are 20 doses of medicine remaining.** Now is the time to get your next PULMICORT TURBUHALER.
- **When the red mark reaches the bottom of the window, your inhaler should be discarded as it may no longer deliver the correct amount of medication.** (You may still hear a sound if you shake it—this sound is not the medicine. This sound is produced by the drying agent inside the Turbuhaler.)
- Remember, you will get a new inhaler each time you refill your prescription.
- **Do not immerse it in water to find out if it is empty. Simply check your dose indicator window.**

FURTHER INFORMATION ABOUT PULMICORT TURBUHALER

- PULMICORT TURBUHALER delivers your medicine as a very fine powder. Because of this, you may not **taste, smell, or feel** any medication entering your lungs when inhaling from PULMICORT TURBUHALER This does not mean that you are not getting your medication.
- PULMICORT TURBUHALER should not be used with a spacer.
- PULMICORT TURBUHALER contains only budesonide and does not contain any inactive ingredients.
- PULMICORT TURBUHALER is specially designed to deliver only one dose at a time, no matter how often you click the brown grip. If you accidentally blow into your inhaler after loading a dose, simply follow the instructions for loading a new dose.

This leaflet does not contain the complete information about your medicine. If you have anyquestions, or are not sure about something, then you should ask your doctor or pharmacist.

You may want to read this leaflet again. Please DO NOT THROW IT AWAY until you have finished your medicine.

REMEMBER: This medicine has been prescribed for you by your doctor. DO NOT give this medicine to anyone else.

USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR DOCTOR.

If you have further questions about the use of PULMICORT TURBUHALER, call: 1-800-236-9933.

Extended Text™ INCIRC™ U.K. Pat. App. Nos. 9019032.3 & 9400832.3, Euro Pat. App. Nos. 91915912.9 & 94200154.6, U.S. Pat. No. 5399403.

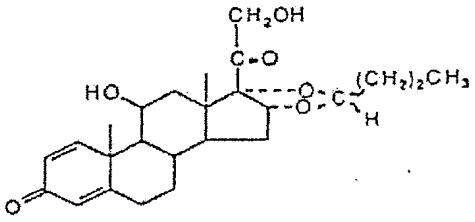
Manufactured for: AstraZeneca LP, Wilmington, DE 19850
By: AstraZeneca AB, Södertälje, Sweden
33020-00
Rev. 10/06 248931

AstraZeneca

ASTRA
ASTRA DRACO

SPECIFICATION

Date	Budesonide micronized	Specification No
95-11-20		22-133-12/9
Product Company Astra Draco		Supersedes Specification No
Issued by Prepared by		22-133-12/8

	Synonyms	16α,17α-Butylidenedioxypregna-1,4-diene-11ß, 21-diol-3,20-dione. S-1320 (laboratory code).
	Structural formula	
	Molecular formula	$C_{25}H_{34}O_6$
	Molecular weight	430.5
	Description	Budesonide is a mixture of two epimeric forms, epimer A and epimer B. A white to off-white fine powder, odourless, freely soluble in chloroform, sparingly soluble in ethanol, practically insoluble in water and in heptane. It melts at 224 °C to 231.5 °C with decomposition. (epimer A:B, 50:50)
		Requirements
1	Appearance	A white to off-white, fine powder.
2	IR-spectrum	Conforms to a reference spectrum.
3	Loss on drying	Not more than 0.5 per cent (m/m).
4	Particle size (Coulter Counter)	The particles will have a mass median diameter of 3 µm or less. At least 85 per cent (m/m) will be particles with a diameter of 5 µm or less.

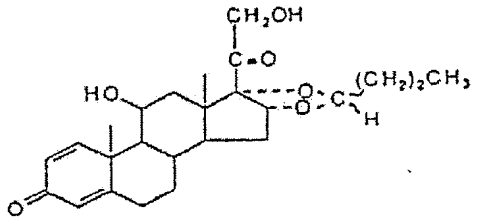
Date 95-11-20 Product Company Astra Draco Issued by Prepared by	Budesonide micronized	Specification No 22-133-12/9 Supersedes Specification No 22-133-12/8

5	Particle size (microscopy)	Not more than 30 individual particles are greater than 10 µm, measured along their longest axis, when 25 fields are investigated at 400-500x magnification. (One drop of a suspension of 20 mg budesonide in 1 g liquid paraffin on the microscope slide.)
6	Organic solvents	Methanol: not more than 0.1 per cent (m/m). Methylene chloride: not more than 0.05 per cent (m/m).
7	Related substances (LC)	Not more than 1.0 per cent in total of known foreign steroids. * No individual known foreign steroid exceeding 0.5 per cent. Not more than 0.5 per cent in total of unknown foreign steroids. No individual unknown foreign steroid exceeding 0.1 per cent. * known foreign steroids are: 16α-hydroxyprednisolone 22-methyl homologue of budesonide D-homobudesonide 21-dehydrobudesonide 14,15-dehydrobudesonide
8	Epimer A	40.0 - 51.0 per cent, determined by LC and related to the content of budesonide.
9	Budesonide	98.0 - 102.0 per cent (m/m), calculated with reference to the dried substance, determined by LC.

ASTRA
ASTRA DRACO

SPECIFICATION

Date		Specification No
97-04-01	Budesonide USA	22-612-17/4
Product Company Astra Draco		Supersedes Specification No
Issued by		22-612-17/3
Prepared by		

	Synonyms	16α,17α-Butylidenedioxypregna-1,4-diene-11ß, 21-diol-3,20-dione. S-1320 (laboratory code).
	Structural formula	
	Molecular formula	$C_{25}H_{34}O_6$
	Molecular weight	430.5
	Description	Budesonide is a mixture of two epimeric forms, epimer A and epimer B. A white to off-white crystalline powder, odourless, freely soluble in chloroform, sparingly soluble in ethanol, practically insoluble in water and in heptane. It melts at 224 °C to 231.5 °C with decomposition (epimer A:B, 50:50).
		Requirements
1	Appearance	A white to off-white crystalline powder.
2	Colour of solution	The absorbance of a 1.5 per cent solution in methanol, determined in a 5 cm cell, is not more than 0.15 at 400 nm 0.04 at 450 nm
3	IR-spectrum	Conforms to a reference spectrum.
4	Loss on drying	Not more than 0.3 per cent (m/m).

Date		Specification No
97-04-01	Budesonide USA	22-612-17/4
Product Company: Astra Draco		Supersedes Specification No
Issued by		22-612-17/3
Prepared by		

5	Organic Solvents	Methanol: not more than 0.1 per cent (m/m). Methylene chloride: not more than 0.05 per cent (m/m).
6	21-acetate of budesonide (LC)	Less than 0.10 %.
7	Other related substances (LC)	Release: Not more than 0.3 per cent in total of specified drug substance related impurities. * Not more than 0.2 per cent in total of unspecified drug substance related impurities. Less than 0.10 per cent of any individual unspecified drug substance related impurity. Shelf life: Not more than 0.4 per cent in total of specified drug substance related impurities. * Not more than 0.4 per cent in total of unspecified drug substance related impurities. Less than 0.10 per cent of any individual unspecified drug substance related impurity. * limits for specified drug substance related impurities at release and shelf life: Not more than 0.2 % of 16α-hydroxyprednisolone Less than 0.10 % of D-homobudesonide Less than 0.10 % of 21-dehydrobudesonide Less than 0.10 % of 14,15-dehydrobudesonide
8	Epimer A	44.0 - 51.0 per cent, determined by LC and related to the content of budesonide.
9	Budesonide	98.0 - 102.0 per cent (m/m), calculated with reference to the dried substance and determined by LC.
10	Microbial quality	Total aerobic microbial count: Not more than 10 cfu/g. Total yeast and mold count: Not more than 2 cfu/g.

Exhibit F

1995

USP 23

NF 18

THE UNITED STATES PHARMACOPEIA

THE NATIONAL FORMULARY

By authority of the United States Pharmacopeial Convention, Inc., meeting at Washington, D.C., March 8–10, 1990. Prepared by the Committee of Revision and published by the Board of Trustees

Official from January 1, 1995

UNITED STATES PHARMACOPEIAL CONVENTION, INC.
12601 Twinbrook Parkway, Rockville, MD 20852

If colonies matching the description in Table 5 are found, proceed with further identification by transferring the suspect colonies individually, by means of an inoculating loop, to the surface of Levine Eosin–Methylene Blue Agar Medium, plated on petri dishes. If numerous colonies are to be transferred, divide the surface of each plate into quadrants, each of which may be seeded from a separate colony. Cover and invert the plates, and incubate. Upon examination, if none of the colonies exhibits both a characteristic metallic sheen under reflected light and a blue-black appearance under transmitted light, the specimen meets the requirements of the test for the absence of *Escherichia coli*. The presence of *Escherichia coli* may be confirmed by further suitable cultural and biochemical tests.

Total Combined Molds and Yeasts Count—Proceed as for the *Plate Method* under *Total Aerobic Microbial Count*, except for using the same amount of Sabouraud Dextrose Agar Medium or Potato Dextrose Agar Medium, instead of Soybean Casein Digest Medium, and except for incubating the inverted petri dishes for 5 to 7 days at 20° to 25°.

Retest—For the purpose of confirming a doubtful result by any of the procedures outlined in the foregoing tests following their application to a 10.0-g specimen, a retest on a 25-g specimen of the product may be conducted. Proceed as directed under *Procedure*, but make allowance for the larger specimen size.

⟨71⟩ STERILITY TESTS

The following procedures are applicable for determining whether a Pharmacopeial article purporting to be sterile complies with the requirements set forth in the individual monograph with respect to the test for *Sterility*. (For the use of sterility test procedures as part of quality control in manufacture, see *Sterilization and Sterility Assurance of Compendial Articles* ⟨1211⟩.) In view of the possibility that positive results may be due to faulty aseptic techniques or environmental contamination in testing, provisions are included under *Interpretation of Sterility Test Results* for two stages of testing.

Alternative procedures may be employed to demonstrate that an article is sterile, provided the results obtained are at least of equivalent reliability. (See *Procedures* under *Tests and Assays* in the *General Notices and Requirements*.) Where a difference appears, or in the event of a dispute, when evidence of microbial contamination is obtained by the procedure given in this Pharmacopeia, the result so obtained is conclusive of failure of the article to meet the requirements of the test. Similarly, failure to demonstrate microbial contamination by the procedure given in this Pharmacopeia is evidence that the article meets the requirements of the test. For additional interpretive information, see *Sterilization and Sterility Assurance of Compendial Articles* ⟨1211⟩.

Media

Media for the tests may be prepared as described below, or dehydrated mixtures yielding similar formulations may be used provided that, when reconstituted as directed by the manufacturer or distributor, they have growth-promoting properties equal or superior to those obtained from the formulas given herein.

I. Fluid Thioglycollate Medium

L-Cystine	0.5 g
Sodium Chloride	2.5 g
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	5.5 g
Agar, granulated (moisture content not in excess of 15%)	0.75 g
Yeast Extract (water-soluble)	5.0 g
Pancreatic Digest of Casein	15.0 g
Sodium Thioglycollate	0.5 g
or Thioglycollic Acid	0.3 mL
Resazurin Sodium Solution (1 in 1000), freshly prepared	1.0 mL
Water	1000 mL

pH after sterilization: 7.1 ± 0.2.

Mix, and heat until solution is effected. Adjust the solution with 1 *N* sodium hydroxide so that, after sterilization, it will have a pH of 7.1 ± 0.2. Filter while hot through filter paper, if necessary. Place the medium in suitable vessels that provide a ratio of surface to depth of medium such that not more than the upper half of the medium has undergone a color change indicative of oxygen uptake at the end of the incubation period. Sterilize in an autoclave. If more than the upper one-third has acquired a pink color, the medium may be restored once by heating in a steam bath or in free-flowing steam until the pink color disappears. When ready for use, not more than the upper one-third of the medium should have a pink color.

Use Fluid Thioglycollate Medium by incubating it under aerobic conditions.

II. Alternative Thioglycollate Medium for Devices Having Tubes with Small Lumina

L-Cystine	0.5 g
Sodium Chloride	2.5 g
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	5.5 g
Yeast Extract (water-soluble)	5.0 g
Pancreatic Digest of Casein	15.0 g
Sodium Thioglycollate	0.5 g
or Thioglycollic Acid	0.3 mL
Water	1000 mL

pH after sterilization: 7.1 ± 0.2.

Heat the ingredients in a suitable container until solution is effected. Mix, and, if necessary, adjust the solution with 1 *N* sodium hydroxide so that, after sterilization, it will have a pH of 7.1 ± 0.2. Filter, if necessary, place in suitable vessels, and sterilize by steam. The medium is freshly prepared or heated in a steam bath and allowed to cool just prior to use. Do not cool.

Use Alternative Thioglycollate Medium in a manner that will assure anaerobic conditions for the duration of the incubation period.

III. Soybean-Casein Digest Medium

Pancreatic Digest of Casein	17.0 g
Papaic Digest of Soybean Meal	3.0 g
Sodium Chloride	5.0 g
Dibasic Potassium Phosphate	2.5 g
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	2.5 g
Water	1000 mL

pH after sterilization: 7.3 ± 0.2.

Dissolve the solids in the water, warming slightly to effect solution. Cool the solution to room temperature, and adjust with 1 *N* sodium hydroxide, if necessary, to obtain a pH of 7.3 after sterilization. Filter, if necessary, and dispense into suitable vessels. Sterilize by steam.

Use Soybean-Casein Digest Medium by incubating under aerobic conditions.

NOTE—Where Fluid Thioglycollate Medium and Soybean-Casein Digest Medium are to be used in *Test Procedure: Direct Transfer to Test Media* applied to a specimen containing penicillin or cephalosporin class of antibiotic, aseptically add to each tube of Medium a quantity of penicillinase sufficient to inactivate the amount of antibiotic in the specimen under test. Determine the appropriate quantity of penicillinase to use for the purpose by using a penicillinase preparation that has been assayed previously for its penicillin- or cephalosporin-inactivating power. Or confirm that the appropriate quantity of penicillinase has been transferred to a tube of Fluid Thioglycollate Medium by adding to it an amount of penicillin or cephalosporin antibiotic equivalent to the amount of antibiotic in the specimen under test, inoculating the Medium with 1 mL of a 1:1000 dilution of an 18- to 24-hour culture of *Staphylococcus aureus* (ATCC 29737) in Fluid Thioglycollate Medium, and incubating it for 24 hours at 30° to 35°; at this time typical microbial growth must be observed. Perform this confirmatory test in an area completely separate from that used for sterility testing.

Diluting and Rinsing Fluids

FLUID A—Dissolve 1 g of peptic digest of animal tissue (*Reagent Specifications* in the section *Reagents, Indicators and Solutions*) in water to make 1 liter, filter or centrifuge to clarify, adjust to a pH of 7.1 ± 0.2, dispense into containers in suitable quantities, and sterilize by steam. [NOTE—Where *Fluid A* is to be used in performing the test for *Sterility* on a specimen

enicillin or cephalosporin class of antibiotics, aseptically add a uantity of sterile penicillinase to the *Fluid A* to be used to rinse e membrane(s) sufficient to inactivate any residual antibiotic tivity on the membrane(s) after the solution of the specimen s been filtered.]

FLUID D—If the test specimen contains lecithin or oil, or for vice sterile pathway tests using membrane filtration, use *Fluid* to each liter of which has been added 1 mL of polysorbate 80, just to a pH of 7.1 ± 0.2, dispense into flasks, and sterilize steam.

FLUID K—

ptic Digest of Animal Tissue (see *Reagent Specifications* in the section *Reagents, Indicators, and Solutions*)	5.0 g
f Extract	3.0 g
lysorbate 80	10.0 g
ter	1000 mL

after sterilization: 6.9 ± 0.2.
ilize by steam.

NOTE—A sterile fluid shall not have antibacterial or antifungal perties if it is to be considered suitable for dissolving, diluting, nsing an article under test for sterility.

Growth Promotion Test

firm the sterility of each lot of medium by incubation of esentative containers, at the temperature and for the length ime specified in the test.

est each autoclaved load of each lot of medium for its growth-moting qualities by separately inoculating duplicate test con-ers of each medium with 10 to 100 viable microorganisms of of the strains listed in the accompanying table, and incu-g according to the conditions specified.

he test media are satisfactory if clear evidence of growth ars in all inoculated media containers within 7 days. The may be conducted simultaneously with the use of the test a for sterility test purposes. The sterility test is considered id if the test medium shows inadequate growth response.

If freshly prepared media are not used within 2 days, store them in the dark, preferably at 2° to 25°.

Finished media, if stored in unsealed containers, may be used for not more than one month, provided that they are tested within one week of the time of use and if the color indicator requirements are met. If stored in suitable sealed containers, the media may be used for not more than one year, provided they are tested for growth promotion every three months and if the color indicator requirements are met.

Bacteriostasis and Fungistasis

Before initiating direct transfer sterility tests on an article, determine the level of bacteriostatic and fungistatic activity by the following procedures. Prepare dilute cultures of bacteria and fungi from at least the strains of microorganisms cited under *Growth Promotion Test*. Inoculate the sterility test media with 10 to 100 viable microorganisms, employing volumes of medium listed in the table of Quantities for Liquid Articles under *Selection of Test Specimens and Incubation*. Add the specified portion of article to half of a suitable number of the containers already containing the inoculum and culture medium. Incubate the containers at the appropriate temperatures and under the conditions listed in the table for not less than 7 days.

If growth of the test organisms in the article-medium mixture is visually comparable to that in the control vessels, use the amounts of article and medium regularly specified in the table of Quantities for Liquid Articles under *Selection of Test Specimens and Incubation*.

If the article is bacteriostatic and/or fungistatic when tested as described above, use a suitable sterile neutralizing agent, if available. Suitability of such an agent is determined as in the test described below. If a neutralizing agent is not available, establish, as described below, suitable amounts of article and medium to be used.

Repeat the tests set forth above, using the specified amount of article and larger volumes of the medium to determine the ratio of article to medium in which growth of the test organisms is not adversely affected.

Medium	Test Microorganisms*	Incubation	
		Temperature (°)	Conditions
d Thioglycollate	(1) *Bacillus subtilis* (ATCC No. 6633)†	30 to 35	
	(2) *Candida albicans* (ATCC No. 10231)	30 to 35	Aerobic
	(3) *Bacteroides vulgatus* (ATCC No. 8482)‡	30 to 35	
rnative Thioglycollate	(1) *Bacteroides vulgatus* (ATCC No. 8482)‡	30 to 35	Anaerobic
n-Casein Digest	(1) *Bacillus subtilis* (ATCC No. 6633)†	20 to 25	
	(2) *Candida albicans* (ATCC No. 10231)	20 to 25	Aerobic

Available from the American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD 20852.
NOTE—Seed lot culture maintenance techniques should be employed so that the viable microorganisms used for inoculation are more than 5 passages removed from the ATCC cultures.
If a spore-forming organism is not desired, use *Micrococcus luteus* (ATCC No. 9341) at the incubation temperatures indicated table.
a spore-forming organism is desired, use *Clostridium sporogenes* (ATCC No. 11437) at the incubation temperature indicated e table.

Quantities for Liquid Articles

Container content (mL)	Minimum volume taken from each container for each medium	Minimum Volume of Each Medium		No. of containers per medium
		Used for direct transfer of volume taken from each container (mL)	Used for membrane or half membrane representing total volume from the appropriate number of containers (mL)	
ss than 10	1 mL, or entire contents if less than 1 mL	15	100	20
to less than 50	5 mL	40	100	20
to less than 100	10 mL	80	100	20
to less than 100, ntended for intravenous administration	Entire contents	—	100	10
0 to 500	Entire contents	—	100	10
er 500	500 mL	—	100	10

If the specified amount of article is bacteriostatic or fungistatic in 250 mL of the medium, decrease the amount of the article to find the maximum amount that does not adversely affect the growth of the test organism in 250 mL of the medium. For liquids and suspensions, if this amount is less than 1 mL, increase the quantity of medium so that the 1 mL is sufficiently diluted to prevent inhibition of growth. For solids that are not readily soluble or dispersible, if the amount is less than 50 mg, increase the quantity of medium so that the 50 mg of the article is sufficiently diluted to prevent inhibition of growth. In either case, use the amounts of the article and medium established in this ratio for sterility testing.

Where membrane filtration is used, make similar comparisons using the specified portions of the article under test and similar quantities of a suitable diluting and rinsing fluid, rinsing the membrane in each case with three 100-mL portions of the diluting and rinsing fluid. Inoculate the stated quantities of viable microorganisms into each final portion of diluting and rinsing fluid used to filter the article under test and to filter the diluting and rinsing fluid only. The growth of the test organism in each case from the membrane(s) used to filter the article under test followed by the inoculated final diluting and rinsing fluid is visually comparable to that from the membrane(s) used to filter only the inoculated diluting and rinsing fluid.

General Procedure

The test procedures include (1) direct transfer to test media and (2) membrane filtration techniques. Sterility testing of Pharmacopeial articles using membrane filtration of the test specimens, where feasible, is the method of choice. The procedure is particularly useful for liquids and soluble powders possessing bacteriostatic or fungistatic properties, so as to permit separation of possible contaminating microorganisms from such growth inhibitors. The procedure is to be validated for such use. For similar reasons, it is very useful where the article is an oil, an ointment, or a cream that can be put into solution with nonbacteriostatic or nonfungistatic diluting fluids. Its use is also entirely appropriate and preferable in the sterility testing of nonbacteriostatic or nonfungistatic liquids or soluble powders. Certain devices also may be appropriately tested for sterility of surfaces or the critical pathways by the membrane filtration technique.

Because of diversity in the nature of articles to be tested and other factors affecting the conduct of the sterility test, it is important to observe the following considerations in performing sterility tests.

OPENING CONTAINERS

Cleanse the exterior surfaces of ampuls and closures of vials and bottles with a suitable decontaminating agent, and gain access to the contents in an aseptic manner. If the vial contents are packaged under vacuum, admit sterile air by means of a suitable sterile device, such as a needle attached to a syringe containing sterilizing grade filter material.

For purified cotton, gauze, surgical dressings, sutures, and related Pharmacopeial articles, open the package or container aseptically.

SELECTION OF TEST SPECIMENS AND INCUBATION

For liquid articles, use not less than the volumes of article and medium for each unit and the number of containers per medium specified in the table of Quantities for Liquid Articles, in this section. If the contents are of sufficient quantity, they may be divided so that portions are added to each of the two specified media. If each container does not contain sufficient volume for both media, use double the number of containers. For articles other than liquids, test 20 units of the article with each medium. For such articles in which only the lumen must be sterile, flush the lumen with a suitable quantity of appropriate medium to yield a recovery of not less than 15 mL of medium.

Unless otherwise directed in the individual monograph or in a section of this chapter, incubate the test mixture for 14 days with Fluid Thioglycollate Medium (or Alternative Thioglycollate Medium, where so indicated) at 30° to 35° and with Soybean-Casein Digest Medium at 20° to 25°.

Test Procedures for Direct Transfer to Test Media

LIQUIDS

Remove liquids from test containers with a sterile pipet or a sterile syringe and needle. Aseptically transfer the specified volume of the material from each test container to a vessel of culture medium. Mix the liquid with the medium, but do not aerate excessively. Incubate in the specified media as directed under *General Procedure* for not less than 14 days. Examine the media visually for growth at least as often as on the third, fourth or fifth day, on the seventh or eighth day, and on the last day of the test period.

Where the material being tested renders the medium turbid so that the presence or absence of microbial growth cannot be determined readily by visual examination, transfer suitable portions of the medium to fresh vessels of the same medium at least once during the period from the third to the seventh day after the test is started. Continue incubation of the original and the transfer vessels for a total of not less than 14 days from the original inoculation.

OINTMENTS AND OILS INSOLUBLE IN ISOPROPYL MYRISTATE

Select 20 representative containers, assign them to 2 groups of 10 containers, and treat each group as follows. Aseptically transfer 100 mg from each of the 10 containers to a flask containing 100 mL of a sterile, aqueous vehicle capable of dispersing the test material homogeneously throughout the fluid. [NOTE—The choice of dispersing agent incorporated into the aqueous vehicle may differ according to the nature of the ointment or oil. Before initiating routine use of a given dispersing agent, test the dispersing agent to ascertain that in the concentration used it has no significant antimicrobial effects during the time interval for all transfers employing test procedures described under *Bacteriostasis and Fungistasis*.] Mix an aliquot of 10 mL of the fluid mixture so obtained with 80 mL of each medium and proceed as directed under *Liquids*, beginning with "Incubate in the specified media."

SOLIDS

Take a quantity of the product in the form of a dry powder, of a solution or a suspension of the product prepared with sterile diluent to the immediate container), corresponding to not less than 300 mg from each container being tested. Use the entire contents if each contains less than 300 mg of solid. Transfer it to not less than 40 mL of Fluid Thioglycollate Medium and to not less than 40 mL of Soybean-Casein Digest Medium, respectively, and mix, the number of containers and the conditions of incubation being the same as for liquids. Proceed as directed under *Liquids*, beginning with "Examine the media visually."

PURIFIED COTTON, GAUZE, SURGICAL DRESSINGS, SUTURES, AND RELATED ARTICLES

From each package of cotton, rolled gauze, or gauze being tested, remove aseptically two or more portions totaling to 500 mg each from the innermost part of the sample. For individually packaged single-use materials such as gauze, remove aseptically a single portion of 250 mg to 500 mg or the entire article in the case of small, i.e., 25- × 75-mm, adhesive absorbent bandages, or sutures.

Aseptically transfer these portions of the article to the required number of containers of appropriate media and incubate as directed under *General Procedure*. Proceed as directed under *Liquids*, beginning with "Examine the media visually."

STERILIZED DEVICES

The following considerations apply to sterilized devices manufactured in lots, each consisting of a number of units. These considerations apply to sterile devices manufactured in lots or in individual units where the self-destructive nature of the Sterility Test renders the conventional Sterility Test unacceptable. For these articles, appropriate and acceptable modifications to the Sterility Test must be made.

articles of such size and shape as to permit complete im-
on in not more than 1000 mL of culture medium, test the
article, using the appropriate media, and incubate as di-
under *General Procedure*. Proceed as directed under *Liq-*
beginning with "Examine the media visually."

devices having hollow tubes, such as transfusion or infusion
blies, or where the size of an item makes immersion im-
able and where only the fluid pathway must be sterile,
he lumen of each of 20 units with a sufficient quantity of
Thioglycollate Medium and the lumen of each of 20 units
sufficient quantity of Soybean-Casein Digest Medium to
recovery of not less than 15 mL of each medium, and
te with not less than 100 mL of each of the two media as
d under *General Procedure*. For devices in which the lu-
so small that Fluid Thioglycollate Medium will not pass
substitute Alternative Thioglycollate Medium for Fluid
ycollate Medium, but incubate the medium anaerobically.
re the entire intact article, because of its size and shape,
be tested for sterility by immersion in not more than 1000
culture medium, expose that portion of the article most
t to sterilize, and test that portion, or where practicable
two or more portions each from the innermost portion of
cle. Aseptically transfer these portions of the article to
cified number of vessels of appropriate media in a volume
more than 1000 mL, and incubate as directed under *Gen-*
cedure. Proceed as directed under *Liquids*, beginning
examine the media visually."

re the presence of the test specimen in the medium in-
with the test because of bacteriostatic or fungistatic ac-
se the article thoroughly with a minimal amount of rinse
e under *Diluting and Rinsing Fluids*). Recover the rinse
id test as directed for *Devices* under *Test Procedures*
Membrane Filtration.

ERILE EMPTY OR PREFILLED SYRINGES

lity testing of prefilled syringes is performed by employing
e techniques used in testing sterile products in vials or
. The direct transfer technique may be employed if the
stasis and Fungistasis determination has indicated no
activity under the test conditions. Where appropriate,
nbrane filtration procedure may be employed. For pre-
ringes containing a sterile needle, flush the contained
through the lumen. For syringes packaged with a sep-
edle, aseptically attach the needle, and expel the product
appropriate media. Pay special attention toward dem-
g that the outside of the attached needle (that portion
ill enter the patient's tissues) is sterile. For empty sterile
take up sterile medium or diluent into the barrel through
le if attached, or if not attached, through a sterile needle
for the purpose of the test, and express the contents into
opriate media.

Procedures Using Membrane Filtration

the membrane filtration technique is used for liquid
hat may be tested by direct transfer to test media, test
han the volumes and numbers specified under *Selection*
Specimens and Incubation.

atus—A suitable membrane filter unit consists of an as-
hat facilitates the aseptic handling of the test articles
allows the processed membrane to be removed asepti-
inoculation of appropriate media or an assembly where
edia can be added to the sealed filter and the membrane
d in situ. A membrane generally suitable for sterility
as a nominal porosity of 0.45 μm, a diameter of approx-
47 mm, and a flow rate of 55 to 75 mL of water per
at a pressure of 70 cm of mercury. The entire unit may
bled and sterilized with the membrane(s) in place prior
the test, or the membranes may be sterilized separately
eans that maintains the performance characteristics of
and assures the sterility of the filter and the assembly.
the article to be tested is an oil, the membrane may be
separately, and after thorough drying, the unit assem-
ng aseptic precautions.

DS MISCIBLE WITH AQUEOUS VEHICLES

ically transfer the volumes required for both media, as
in the table of Quantities for Liquid Articles under *Selection of Test Specimens and Incubation*, either directly into one or two separate membrane filter funnels or to separate sterile pooling vessel(s) prior to transfer. In the case of liquid articles in containers in which the volume of liquid is either less than 50 mL, or 50 mL to less than 100 mL, and not intended for intravenous administration, the required volumes from not less than 20 containers are thus represented by one membrane, or membrane half, transferred to each medium. If the volume of liquid in the article is 50 mL to less than 100 mL per container and is intended for intravenous administration, or is 100 mL or more up to 500 mL, aseptically transfer the entire contents of not less than 10 containers through each of two filter assemblies, or not less than 20 containers if only one filter assembly is used. If the volume of the liquid in the article is more than 500 mL, aseptically transfer not less than 500 mL from each of not less than 10 containers through each of two filter assemblies, or not less than 20 containers if only one filter assembly is used. Immediately pass each specimen through the filter with the aid of vacuum or pressure.

In some cases, where the liquid is highly viscous and not readily filterable through one or two membranes, more than two filter assemblies may be needed. In such cases, half the number of membranes used are incubated in each medium, provided that the volumes and requirements for numbers of containers per medium are complied with. If the product is bacteriostatic or fungistatic, rinse the membrane(s) with three 100-mL portions of *Fluid A*.

Aseptically remove the membrane(s) from the holder(s), cut the membrane in half (if only one is used), immerse the membrane, or one-half of the membrane, in 100 mL of Soybean-Casein Digest Medium, and incubate at 20° to 25° for not less than 7 days. Similarly, immerse the other membrane, or other half of the membrane, in 100 mL of Fluid Thioglycollate Medium, and incubate at 30° to 35° for not less than 7 days.

NOTE—Where the product under test has inherent bacteriostatic properties, use hydrophobic membrane filter disks, or after the specimen has been filtered, cut a disk comprising about one-half of the filtering area from the center of the membrane using a sterile cutting device, aseptically transferring the disk cut from the center of the membrane to Fluid Thioglycollate Medium, and aseptically transferring the remainder of the disk to Soybean-Casein Digest Medium.

LIQUIDS IMMISCIBLE WITH AQUEOUS VEHICLES (LESS THAN 100 mL PER CONTAINER)

Using the contents of not less than 20 containers (40 containers, if each one does not contain sufficient volume for both media), aseptically transfer the volumes required for both media, as indicated in the table of Quantities for Liquid Articles under *Selection of Test Specimens and Incubation*, either directly into one or two separate membrane filter funnels or to separate sterile pooling vessels prior to transfer. The required volumes from not less than 20 containers are thus represented by the membrane, or membrane half to be transferred to each medium. Immediately pass each specimen through the filter with the aid of vacuum or pressure.

If the substance is a viscous liquid or suspension and not adaptable to rapid filtration, aseptically add a sufficient quantity of diluting fluid to the pooled specimen prior to filtration to increase the flow rate.

If the product under test has inherent bacteriostatic or fungistatic properties or contains a preservative, wash the filter with from one to three 100-mL portions of *Fluid A*. If the substance under test contains lecithin or oil, substitute *Fluid D* for *Fluid A*.

Upon completion of the filtration and rinsing, treat the membrane(s) as directed under *Liquids Miscible with Aqueous Vehicles*, beginning with "Aseptically remove the membrane(s)."

FILTERABLE SOLIDS

Take about 6 g of the product in the form of a dry solid (or a portion of a solution or suspension of the product, prepared by adding sterile diluent to the immediate container(s), corresponding to 6 g of solid), or not less than 300 mg from each container being tested, or the entire contents of each container if each contains less than 300 mg of solids, unless otherwise specified in

the individual monograph, the number of containers being the same as specified for *Liquids Miscible with Aqueous Vehicles*. Transfer the specimen aseptically to a vessel containing 200 mL of *Fluid A*, and swirl to dissolve. If the specimen does not dissolve completely, use 400 mL of *Fluid A*, or divide the specimen aseptically into two portions and test each using 200 mL of *Fluid A*. Aseptically transfer the solution(s) into one or two membrane funnels, and immediately filter with the aid of vacuum or pressure. If the product under test has inherent bacteriostatic or fungistatic properties, rinse the membrane(s) with three 100-mL portions of *Fluid A*. Upon completion of the filtration and rinsing, treat the membrane(s) as directed under *Liquids Miscible with Aqueous Vehicles*, beginning with "Aseptically remove the membrane(s)."

OINTMENTS AND OILS SOLUBLE IN ISOPROPYL MYRISTATE

Dissolve not less than 100 mg from each of not less than 20 containers (40 containers, if each one does not contain sufficient volume for both media) in not less than 100 mL of isopropyl myristate with a pH of water extract not less than 6.5 (see under *Reagent Specifications* in the section *Reagents, Indicators, and Solutions*), which previously has been rendered sterile by filtration through a 0.22-μm membrane filter. [NOTE—Warm the sterilized solvent, and if necessary the test material, to not more than 44° just prior to use.] Swirl the flask to dissolve the ointment or oil, taking care to expose a large surface of the material to the solvent. Filter the dissolved ointment promptly following dissolution. Aseptically transfer the mixture into one or two membrane filter funnels. Immediately pass each specimen through the filter with the aid of vacuum or pressure. Keep filter membrane(s) covered with liquid throughout the filtration for maximum efficiency of the filter.

Following filtration of the specimen, wash the membrane(s) with two 200-mL portions of *Fluid D*, then wash with 100 mL of *Fluid A*. Treat the test membrane(s) as directed under *Liquids Miscible with Aqueous Vehicles*, beginning with "Aseptically remove the membrane(s)," except to provide that the sterility test medium to be used contains 1 g of polysorbate 80 per liter.

If the substance under test contains petrolatum, use *Fluid K*. Moisten the membrane(s) with approximately 200 μL of the rinse medium before the filtration operation begins, and keep the membrane(s) covered with liquid throughout the filtration operation for maximum efficiency of the filter.

Following filtration of the specimen, wash the membrane(s) with three 100-mL portions of the rinse medium. Treat the test membrane(s) as directed above.

NOTE—For ointments and oils that are insoluble in isopropyl myristate, proceed as directed for *Ointments and Oils Insoluble in Isopropyl Myristate* under *Test Procedures for Direct Transfer to Test Media*.

NONFILTERABLE SOLIDS

The sterility testing of these articles by membrane filtration is considered inadvisable unless it can be demonstrated that filter blockage does not occur. Proceed as directed for *Solids* under *Test Procedures for Direct Transfer to Test Media*.

DEVICES

Devices that are purported to contain sterile pathways may be tested for sterility by the membrane filtration technique as follows.

Aseptically pass a sufficient volume of *Fluid D* through each of not less than 20 devices so that not less than 100 mL is recovered from each device. Collect the fluids in aseptic containers, and filter the entire volume collected through membrane filter funnel(s) as directed under *Liquids Miscible with Aqueous Vehicles*, beginning with "Aseptically remove the membrane(s)."

Where the devices are large, and lot sizes are small, test an appropriate number of units as described for similar cases in the section *Sterilized Devices* under *Test Procedures for Direct Transfer to Test Media*.

Interpretation of Sterility Test Results

FIRST STAGE

At the prescribed intervals during and at the conclusion of the incubation period, examine the contents of all of the vessels for evidence of microbial growth, such as the development of turbidity and/or surface growth. If no growth is observed, the article tested meets the requirements of the test for sterility.

If microbial growth is found, but a review in the sterility testing facility of the monitoring, materials used, testing procedures and negative controls indicates that inadequate or faulty aseptic technique was used in the test itself, the *First Stage* is declared invalid and may be repeated.

If microbial growth is observed but there is no evidence for invalidating the *First Stage* of the test, proceed to the *Second Stage*.

SECOND STAGE

The minimum number of specimens selected is double the number tested in the *First Stage*. The minimum volumes tested of each specimen and the media and incubation periods are the same as those indicated for the *First Stage*. If no microbial growth is found, the article tested meets the requirements of the test for sterility. If growth is found, the result so obtained is confirmed that the article tested fails to meet the requirements of the test for sterility. If, however, it can be demonstrated that the *Second Stage* was invalid because of faulty or inadequate aseptic technique in the performance of the test, the *Second Stage* may be repeated.

NOTE—Where sterility testing is used as part of an assessment of a production lot or batch or as one of the quality control tests for release of such lot or batch, see *Sterilization and Assurance of Compendial Articles* ⟨1211⟩.

Biological Tests and Assays

⟨81⟩ ANTIBIOTICS—MICROBIAL ASSAYS

The activity (potency) of antibiotics may be demonstrated under suitable conditions by their inhibitory effect on microorganisms. A reduction in antimicrobial activity also will reveal changes not demonstrable by chemical methods. Accordingly, microbial or biological assays remain generally the standard in resolving doubt with respect to possible loss of activity. This chapter summarizes these procedures for the antibiotics recognized in this Pharmacopeia for which microbiological assay remains the definitive method.

Two general methods are employed, the cylinder-plate (or "cup") assay and the turbidimetric or "tube" assay. The first is based upon diffusion of the antibiotic from a vertical cylinder through a solidified agar layer in a petri dish or plate to an extent such that growth of the added microorganism is prevented entirely in a circular area or "zone" around the cylinder containing a solution of the antibiotic. The turbidimetric method depends upon the inhibition of growth of a microbial culture in a uniform suspension of the antibiotic in a fluid medium that is favorable to bacterial growth in the absence of the antibiotic.

APPARATUS

All equipment is to be thoroughly cleaned before each use. Glassware for holding and transferring test solutions is sterilized by dry heat or by steam.

VALIDATION

The sterilization or aseptic processing of an HSD should be in accordance with properly designed and validated written procedures. The act of validation of a sterilization or aseptic process involves planned testing designed to demonstrate that microorganisms will be effectively destroyed, removed, or prevented from inadvertently being introduced by personnel or by process-related activities.

Sterilization Processes

A high-risk HSD prepared from nonsterile ingredients or components should be sterilized using an appropriate sterilization process, such as filtration or heat sterilization. In general, each sterilization process should be validated to demonstrate suitability for its intended purpose and specific manner of intended uses.

STERILIZATION BY FILTRATION

The sterilizing filtration process should be capable of removing microorganisms from the liquid HSD. Commercially available sterilized filtration devices should be certified to be appropriate for human use in sterile pharmaceutical applications, have a pore size of 0.2 μm or smaller (generally recognized as a sterilizing filter), and have been lot tested for retention of *Pseudomonas diminuta* at a minimum concentration of 10^7 organisms per cm^2 under specified operating parameters. The individual devices should be tested for membrane and housing integrity, pyrogenicity, and extractables by the manufacturer. Such devices should be capable of sterilizing an HSD (see *Sterilization and Sterility Assurance of Compendial Articles* ⟨1211⟩). Before using such devices, the pharmacist should thoroughly evaluate the suitability for the intended HSD and conditions of use. The size and configuration of filtration devices should accommodate the volume being filtered to permit complete filtration in a reasonable period of time and without clogging to the point where mid-process filter changes would be required.

Filters and associated devices and apparatus (housing, gaskets, etc.) should be physically and chemically compatible with the product to be filtered and should be capable of withstanding the temperatures, pressures, and hydrostatic stresses imposed on the system. These capabilities are to be established through appropriate product-specific testing. To establish compatibility, the pharmacy may rely on vendor certification or on definitive evidence specific to product and filter, obtained from a critical review of the literature or from reliable unpublished research.

Validation should be established experimentally for all filtration apparatus involving assembly in the pharmacy of the membrane (filtration medium) into its housing or holder. The pharmacy may rely on vendor certification of validation for commercially available presterilized ready-to-use filter devices or pharmacy-assembled apparatus. (The sterilization process used for pharmacy-assembled apparatus must be properly validated.) When relying on vendor certification of filtration validation, the pharmacy should request data from the vendor sufficient to ensure that an adequate challenge was used (minimum concentration of 10^7 organisms *Pseudomonas diminuta* per cm^2 of filter surface); and to ensure that the filtration apparatus and configuration, duration of filtration, filtration operating conditions (filtration rate and temperature), and the critical product formulation parameters (pH, viscosity, ionic strength, and osmolarity) do not generate the supplied data are representative of the pharmacy's product, apparatus, specified operating parameters, etc., with regard to the factors that might physically or chemically alter the filter integrity, affect microbial capture mechanisms, or shrink or distort the microorganism during filtration.

Each filter device used for product sterilization should be tested for integrity at the time of use. Integrity testing of commercially available, sterile, self-contained filter devices requiring no preuse assembly may be performed at the conclusion of the filtration process. Filter integrity test kits suitable for pharmacy use (for example, those consisting of a small gauge pressure three-way stopcock assembly) are commercially available for testing the bubble point of small disk-type filters. For pharmacy-assembled apparatus, as defined above, prefiltration integrity testing is recommended in addition to postfiltration testing. Quantitative integrity testing, such as the bubble-point or forward flow tests (see *Sterilization and Sterility Assurance of Compendial Articles* ⟨1211⟩) should be used, as appropriate for larger filtration devices or when *Category II* high-risk HSDs are sterilized.

Filtration should be performed in accordance with written procedures that list those filters determined to be acceptable for the various HSDs to be filtered in the pharmacy or in accordance with master batch formulas that include definitive filter specifications. Filtration procedures and master batch formulas should also describe acceptable techniques for using and for checking the integrity of all listed filters. Fluid-filter compatibility must be established prior to the filtration of any HSD not included in the procedure.

HEAT STERILIZATION

Terminal sterilization should be used when sterilizing *Category II* high-risk HSDs. Sterilization may be accomplished in the final sealed container as a validated, controlled moist heat process (see *Sterilization and Sterility Assurance of Compendial Articles* ⟨1211⟩). In the absence of heat sterilization capabilities, or where heat labile drug products or container-closure systems preclude heat sterilization, an HSD may be sterilized by filtration and aseptically processed and controlled in accordance with the standards set forth in this chapter.

Heat sterilization processes should be validated to ensure that the likelihood of survival of the most resistant microorganisms likely to constitute product bioburden is no greater than 10^{-6} under the specified operating conditions and parameters, such as sterilization time and temperature, size and nature of load, and chamber loading configuration. The validation and monitoring of heat sterilization processes should be in writing with all critical parameters specified, should be followed each time of use, and should be supervised by a pharmacist knowledgeable of the technology involved in the sterilization of drug products. Monitoring data should be recorded properly to ensure, retrospectively, that the processes were carried out as specified and that all critical parameters were within specified limits during processing.[1]

Aseptic Processing

All aseptic processing operations and configurations should be adequately established by media-fill validation.[2] Media fills should simulate as closely as possible actual aseptic operations. All manipulations, handling, environmental conditions, and other factors likely to influence the risk of process-associated contamination should be represented by the media-fill simulations. The intensity of such challenges should represent the greatest risk that would be expected during normal production. Media-fill validations should be repeated with sufficient frequency to ensure the ongoing capability of performing properly each aseptic processing operation used in the pharmacy. The frequency and results of media-fill runs should be documented.

The culture medium selected should be capable of supporting the growth of a broad spectrum of microorganisms likely to be production-associated contaminants in the pharmacy. Commercially available media can be obtained that, when reconstituted as directed by the manufacturer, are certified to have growth-promoting properties. Soybean-Casein Digest Medium is acceptable (see *Sterility* ⟨71⟩). Incubation of medium-filled units should take at least 14 days and may be at room temperature for 14 days or may be at room temperature for the first 7 days, with the final 1 to 7 days at 30° to 35°. Alternate suitable incubation schedules may be used as determined by the pharmacy to ensure enough growth of any potential contaminating microorganisms to be visually detectable. Microorganisms in all medium-filled units showing visible evidence of microbial growth should be promptly identified, and if this growth exceeds the action limits, an immediate investigation should be made with prompt correction of any identifiable causes of the failure. Review of environmental monitoring data obtained during the media fill should be included in the investigation, as well as a review of the cleaning, sanitizing, disinfection, production procedures,

[1] PDA Technical Monograph No. 1, Validation of Steam Sterilization Cycles, 1978.

[2] FDA Guideline on Sterile Drug Products Produced by Aseptic Processing, June 1987, pp. 20–27; PDA Technical Monograph No. 2, Validation of Aseptic Filling for Solution Drug Products, 1980.

aseptic technique, personnel practices, and other factors as appropriate. Revalidation should occur after all media-fill failures (see Table 1).

Low-Risk Operations

The primary objective of the validation of aseptic processing involving low-risk operations is to ensure that personnel are capable of using effective aseptic technique to compound an HSD successfully under the most rigorous conditions encountered during normal work assignments. In carrying out validation of the process, personnel should perform media fills consisting of a planned repetitive sequence of compounded or repackaged units. The number of manipulations of each unit and the number of units in each media fill should reflect the most complex and prolonged aseptic manipulations likely to be encountered by an operator as a normal workload requirement. The number of units per media-fill run should be enough to ensure that the operator is capable of replicating acceptable aseptic procedures. Media transfers could be used to represent procedures such as syringe transfers, use of automated compounding devices, multiple additive procedures, and various aseptic assemblies and connections (see *Example of a Validation Procedure for Low-risk Operations*).

EXAMPLE OF A VALIDATION PROCEDURE FOR LOW-RISK OPERATIONS

Scenario—A pharmacy prepares antibiotics, hydration solutions, and parenteral nutrition solutions for home use. The most complex and prolonged aseptic manipulations are required for the parenteral nutrition solutions. The parenteral nutrition solution is made by combining the amino acid and dextrose by gravity transfer into 2-liter empty flexible bags, and then adding a maximum of 10 additives to a bag via syringe transfer. Typically, the pharmacy prepares no more than a 2- or 3-week supply of the solutions at one time.

Example of a validation procedure—One hundred mL of sterile Soybean Casein Digest Medium is transferred via gravity into plastic bags. Twenty units are completed in this manner, to approximate the number of units typically compounded at one time. After all twenty units have been filled, the media containers are lined up in pairs. One mL of media is drawn from one container and transferred aseptically by syringe transfer to another media unit and repeated for a total of ten transfers. Then media from the other units is syringe transferred to the first unit for a total of ten syringe transfers. This process is continued until all twenty units have undergone ten syringe transfers. The media fill units are incubated at room temperature for a total of fourteen days, with frequent checks for growth.

Media fills should be representative of peak periods of fatigue, stress, and pacing demands. For example, media fills could be scheduled immediately after normal production activity has ended. Media fills should not be performed during normal production.

Operators should pass an initial validation, performing three media fills with no contamination, before they are allowed to make HSDs for patients. Subsequently, each operator should perform at least one media fill involving low-risk operations quarterly. If one contaminated unit results from a media fill, the operator should be retrained and then perform three consecutive media fills with no contaminated unit before again being allowed to compound HSDs for patients. Operators should also be revalidated if the nature of their aseptic compounding assignments changes to the extent that their previous media fills are not representative of their revised assignments.

High-Risk Operations

In the case of high-risk operations, the focus of validation is on the process as well as personnel capability. Thus, the primary objective of the validation of aseptic processing for high-risk operations is to ensure that the aseptic process is capable of being carried out consistently under control by any qualified operator before the process is utilized for production of units intended for administration to patients. Accordingly, each type of high-risk operation should be validated independently, rather than having operators perform representative sets of aseptic activities as is the case with low-risk aseptic operations.

Personnel assigned to high-risk aseptic operations should be validated for low-risk operations as described above. In addition, these personnel should participate at least annually in the validation of each high-risk aseptic operation to which assigned.

For example, for high-risk operations involving nonsterile components, the media-fill run should simulate as closely as possible the most intensive conditions likely to be encountered during normal production activities. The number of units in a media-fill run should be no less than the largest number of units encountered during production involving the process being validated. However, the fill volume of media-fill units need not exceed the fill volume of finished product units.

A media-fill run should be performed at least annually for each unique high-risk batch processing procedure and configuration. A media-fill failure for most home care operations (less than 5000 units) is one or more contaminated units after incubation. For batches equal to or greater than 1000 units, a media-fill failure is greater than one contaminated unit. When a media-fill failure occurs, three consecutive successful media fills should occur before the process failing the media fill may be used for the compounding of an HSD for patients.

ENVIRONMENTAL QUALITY AND CONTROL

Achieving and maintaining sterility and overall freedom from contamination of a pharmaceutical product is dependent upon the quality status of the components incorporated, the facility utilized, personnel performance, and the environmental conditions under which the process is performed. The standards required for the environmental conditions depend upon the

Table 1. Validation of Aseptic Processing.

Validation Purpose	Validation Requirements	
	Low Risk	High Risk*
General	Personnel validation	Process validation
Initial	3 consecutive media-fill runs without contamination	3 consecutive media-fill runs without contamination
Revalidation	1 media-fill run quarterly without contamination	annual media-fill run without contamination
Failure revalidation	3 consecutive media-fill runs without contamination	3 consecutive media-fill runs without contamination

* NOTE—Personnel should have first passed low-risk validation.

xposure of the HSD to the immediate environment anticipated ing processing. The quality and control of environmental con- ons for low-risk and high-risk operations is explained in this ion. In addition, operations using nonsterile components re- e the use of a method of preparation designed to produce a ile product.

Critical Site Exposure

he degree of exposure of the product during processing will ffected by the length of time of exposure, the size of the ical site exposed, and the nature of the critical site.

critical site is any opening providing a direct pathway be- n a sterile product and the environment or any surface com- in direct contact with the product and the environment. The of such a site picking up contamination from the environment eases with time of exposure. Therefore, the processing plan the intent of the operator should give due consideration to ization, efficiency, and speed in order to keep such exposure minimum. For example, an ampul should not be opened arily in advance of use.

e size of the critical site affects the risk of contamination ing the product: the greater the exposed area, the greater isk. An open vial or bottle exposes to contamination a critical much larger area than the tip of a 26-gauge needle. There- he risk of contamination when entering an open vial or much greater than during the momentary exposure of a e tip.

e nature of a critical site also affects the risk of contami- n. The relatively rough, permeable surface of a rubber clo- retains microorganisms and other contaminants, after wiping an alcohol pad, more readily than does the smooth glass ce of the neck of an ampul. Therefore, the surface disin- n can be expected to be more effective for an ampul.

e prevention or elimination of airborne particles must be high priority. Mobile or airborne contaminants are much likely to reach critical sites than contaminants that are ing to the floor or other surfaces below the work level. er, particles that are relatively large or of high density settle the airspace more quickly and thus can be removed from cinity of critical sites.

Environmentally Controlled Workspaces

LAFW AND BUFFER ROOM

nvironmentally controlled workspace suitable for the asep- ssing of an HSD consists of a suitably constructed, prop- unctioning, and regularly certified device, which sweeps the pace or an entire room with HEPA-filtered air at a velocity feet per minute ± 20%, such as a laminar airflow workbench W). Such a workspace is required for both low-risk and sk operations. The air blower for the workspace should be l without interruption in order to sweep the workspace ally. Since the airflow velocity is relatively gentle, an must be located in an environmentally controlled room pace otherwise separated from less controlled work areas, s the main pharmacy, by partitions, plastic curtains, or

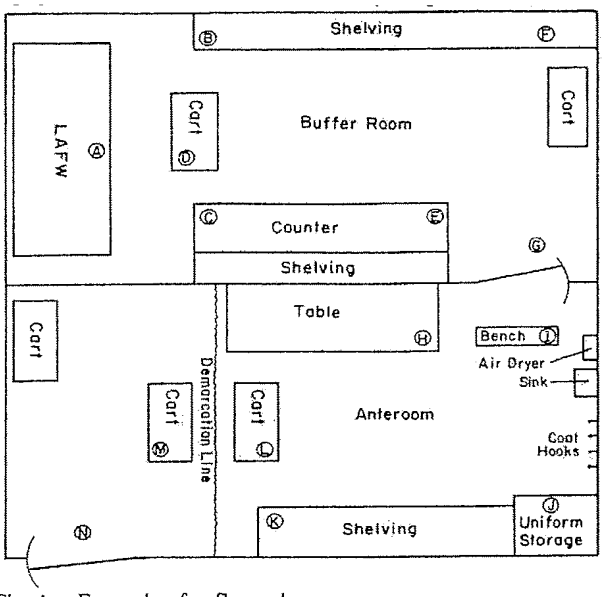


Fig. 1. Example of a floor plan.
(Encircled letters are suggested environmental sampling sites.)

preferably, a solid wall. Hereinafter, this area surrounding an LAFW shall be called the "Buffer Room." (Figure 1 shows an example of a floor plan for an environmentally controlled workspace and adjacent areas, as a basis for illustrating the following discussion.) Clean and sanitized supplies may be accumulated and stored for a limited period of time in the Buffer Room in order to be conveniently available for use in preparing products in the LAFW.

Since an LAFW is normally a self-contained unit, the air circulated is drawn from the Buffer Room and does not contribute fresh air. Therefore, such a unit does not create positive air pressure in the Buffer Room. However, units can be installed to draw in fresh outside air through an HEPA filter and provide positive air pressure, but they cannot be movable.

The direction of flow may be horizontal or vertical. (A suitable biological safety cabinet with vertical airflow should be used for processing cytotoxic and other hazardous agents to protect the operator as well as the product.) The air quality within the LAFW adjacent to critical sites should meet a Class 100 (MCB-1) clean room specification during normal work activity. (See Table 2 for the definition of clean room classes. Also, see *Microbiological Evaluation and Classification of Clean Rooms and Clean Zones* ⟨1116⟩.)

The environmental quality within the Buffer Room should be demonstrably better than that of adjacent areas, such as the main pharmacy, to reduce the risk of contaminants being blown, dragged, or otherwise introduced into the LAFW. For example, strong air currents from briefly opened doors, personnel walking

Table 2. Class Limits in Particles per Cubic Foot.
(Size equal to or greater than particle sizes shown.)*

	Measured Particle Size (micrometers)				
Class	0.1	0.2	0.3	0.5	5.0
1	35	7.5	3	1	—
10	350	75	30	10	—
100	—	750	300	100	—
1,000	—	—	—	1,000	7
10,000	—	—	—	10,000	70
100,000	—	—	—	100,000	700

* The Class limit particle concentrations shown in Table 2 are defined for class purposes only and do not necessarily represent the size distribution to be found in any particular situation. Federal Standard No. 209E, General Services Administration, Washington, DC 20407, September 11, 1992.

past the LAFW, or the airstream from the heating, ventilating, and air-conditioning (HVAC) system can easily exceed the velocity of clean air from the LAFW. Also, operators introducing supplies into the LAFW or reaching in with their arms can drag contaminants along with those movements.

The level of cleanliness of the air in the Buffer Room, in conjunction with the expertise of the operator, is critical to maintaining the Class 100 (MCB-1) conditions within the LAFW. The air entering the Buffer Room should be fresh, HEPA-filtered, conditioned air. The air in the Buffer Room should meet the requirements for at least a Class 100,000 (see Table 2) clean room for low-risk operations and a Class 10,000 (MCB-2) for high-risk operations. In addition to cleaning the inflowing air and providing at least 10 air changes per hour, cooling is essential because of the continual buildup of heat from the circulation of air through the blower and HEPA filter of the LAFW. It should be noted that the circulation of air from the Buffer Room through the HEPA filter of the LAFW enhances the cleanliness of the air, particularly during nonuse periods.

Tasks carried out within the Buffer Room should be limited to those for which a controlled environment is necessary. Only the furniture, equipment, supplies, and other goods required for the tasks to be performed may be brought into this room, and they should be nonpermeable, nonshedding, and resistant to disinfectants. Whenever such items are brought into the room, they should first be cleaned and sanitized. Whenever possible, equipment and other items used in the Buffer Room should not be taken from the room except for calibration, servicing, or other activity associated with the proper maintenance of the item.

The surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets in the Buffer Room should be smooth, impervious, free from cracks and crevices, and nonshedding, thereby promoting cleanability and minimizing spaces in which microorganisms and other contaminants may accumulate. The surfaces should be resistant to damage by sanitizing agents. Junctures of ceilings to walls should be coved or caulked to avoid cracks and crevices where dirt can accumulate. If ceilings consist of inlaid panels, the panels should be impregnated with a polymer to render them impervious and hydrophobic, and they should be caulked around each perimeter to seal them to the support frame. Walls may be of panels locked together and sealed or of epoxy-coated gypsum board. Preferably, floors are overlaid with wide sheet vinyl flooring with heat-welded seams and coving to the sidewall. Dust-collecting overhangs, such as ceiling utility pipes, or ledges, such as window sills, should be avoided. The exterior lens surface of ceiling lighting fixtures should be smooth, mounted flush, and sealed. Any other penetrations through the ceiling or walls should be sealed.

The Buffer Room should contain no sinks or floor drains. Work surfaces should be constructed of smooth, impervious materials, such as stainless steel or molded plastic, so that they are readily cleanable and sanitizable. Carts should be of stainless steel wire or sheet metal construction with good quality, cleanable casters to promote mobility. Storage shelving, counters, and cabinets should be smooth, impervious, free from cracks and crevices, nonshedding, cleanable, and sanitizable. Their number, design, and manner of installation should promote effective cleaning and sanitizing.

ACCESS CONTROL TO THE BUFFER ROOM (ANTEROOM)

Access to the Buffer Room should be planned and strictly controlled because of the need to protect the aseptic operations performed in an LAFW from contaminating substances, while permitting supplies and personnel to enter the area from relatively uncontrolled storerooms, from the main pharmacy, or from administrative areas. Access should be strictly limited to only designated, qualified personnel. The number of personnel in the Buffer Room at any one time should not exceed those essential to perform the required tasks.

An Anteroom or other separated area should be available for the decontamination of supplies, equipment, and personnel before they enter the Buffer Room. (This decontamination area is hereafter referred to as the Anteroom, as shown in Figure 1.) The size of the room should be sufficient to accommodate this activity with the heaviest work load anticipated. Minimally this would require space for two or more carts and space for personnel to clean, sanitize, and transfer supplies from the stockroom cart to the clean room cart. A floor demarcation should identify the maximum distance into the room that stockroom carts[3] may penetrate.

The Anteroom should also be designed for uncartoning and disinfecting large-volume parenteral (LVP) bottles, pouches of hypodermic syringes, ampuls, vials, pouches of LVP bags, transfer set packages, and other required supplies. Here, also, supplies for use in the Buffer Room should be cleaned and disinfected.

One or more sinks and a forced air hand dryer or dispensers of nonshedding towels should be available near the entrance to the Buffer Room so that personnel can scrub their hands and arms before donning hair covers, shoe covers, clean gowns, and face masks. After donning hair and shoe covers, foamed alcohol may be used to resanitize the hands. Faucet handles should be designed so that they can be shut off with the elbows or knees. An alternate procedure being used increasingly is to disinfect the hands and arms with a foamed alcohol, or other effective sanitizer, instead of scrubbing with detergent and water. The forced air hand dryer is then not needed. A means of demarcation should be provided between the Buffer Room side and the general clean side of the Anteroom to enhance the gowning procedure. As an option, a movable bench (preferably of stainless steel), as shown in Figure 1, provides a barrier and place for personnel to sit down to don shoe covers just before entering the Buffer Room. A clean storage area for clean gowning supplies should be conveniently located nearby. The door into the Buffer Room should be closed automatically, positively closed and capable of being opened by elbow hooks or other means without using clean hands. The Anteroom should be designed to reduce to as low as possible the chance of recontamination of cleaned and sanitized supplies and personnel prior to entry into the Buffer Room.

An Anteroom as just described is necessary for high-risk operations. For low-risk operations, a carefully controlled area adjacent to the Buffer Room but without rigid walls may be acceptable. However, essentially the same attention for organization and cleanliness of the anteroom area is to be given in connection with both high- and low-risk operations.

Cleaning and Sanitizing the Workspaces

The cleaning, sanitizing, and organizing of the LAFW should be the responsibility of trained operators (pharmacists and technicians) following written procedures and should be performed at the beginning of each shift. All items should be removed from the LAFW and all surfaces wiped clean with a freshly prepared mild detergent followed by an approved sanitizing agent, allowing sufficient time for the agent to exert its antimicrobial effect. The chosen sanitizing agent should be rotated with one of a different action at least quarterly. Recleaning should be performed if spillage or other events indicate the need.

Work surfaces near the LAFW in the Buffer Room should be cleaned in a similar manner, including counter tops and mobile carts. Storage shelving should be emptied of all supplies, then cleaned and sanitized at least weekly, using approved agents.

Floors in the Buffer Room should be cleaned by mopping daily when no aseptic operations are in progress. Mopping should be performed by trained and supervised custodial personnel using approved agents described in the written procedures. Only approved cleaning and sanitizing agents should be utilized after careful consideration of compatibilities, effectiveness, and inappropriate or toxic residues. Their schedules of use and methods of application should be in accord with written procedures. Wiping cleaning tools, such as wipers, sponges, and mops, should be nonshedding and dedicated to use in the Buffer Room. Wipers and mops may be used in both the Buffer Room and the Anteroom, but only in that order. Most wipers should be discarded after one use. If cleaning tools are reused, their cleanliness should be maintained by thorough rinsing and sanitization after use and storing in a clean environment between uses. Trash should be collected in suitable plastic bags and removed with minimal agitation.

In the Anteroom supplies and equipment removed from shipping cartons should be wiped with a sanitizing agent, such as sterile 70% isopropyl alcohol (IPA[4]), which is checked

[3] Approved by the pharmacist in charge.

[4] NOTE—70% isopropyl alcohol (IPA) may harbor resistant microbial spores. Therefore, IPA used in aseptic areas should always be filtered through a 0.2-μm hydrophobic filter to keep it sterile.

for contamination. Alternatively, if supplies are planned to received in sealed pouches, the pouches can be removed as supplies are introduced into the Buffer Room without the to sanitize the individual supply items. No shipping or other rnal cartons may be taken into the Buffer Room. Cleaning sanitizing of the Anteroom should be performed at least dly by trained and supervised custodial personnel, in accord- with written procedures. However, floors are cleaned and tized daily, always proceeding from the Buffer Room to the room. Storage shelving should be emptied of all supplies cleaned and sanitized at planned intervals, preferably monthly. hese cleaning and sanitizing procedures apply to both low- and high-risk operations.

Personnel and Gowning

ersonnel are critical keys to the maintenance of asepsis when ing out their assigned responsibilities. They must be thor- ly trained in aseptic techniques and be highly motivated to ain these standards each time they prepare a sterile product. to entering the Buffer Room, operators should remove lab jackets or the like, makeup, and jewelry and should oughly scrub hands and arms to the elbow. After drying nds and arms they should properly don clean, nonshedding rm components, including hair covers, shoe covers, knee- h coats or coveralls, and sterile latex gloves, in that order. ats should fit snugly at the wrists and be zipped or snapped in the front. Shoe covers should be donned so that feet touch the floor only on the clean side of the bench or other arcation. Face masks should be donned just prior to begin- work at the horizontal LAFW, as talking, sneezing, or cough- normally generates an air velocity that exceeds the velocity from the LAFW. When working at a vertical LAFW, the ng of a mask is optional where a solid transparent shield nishes a physical barrier between the face of the operator the workspace. However, any facial hair should be com- y covered in all instances.

erile latex gloves should be put on, aseptically—being sure otect the outer surfaces from contamination—as the last rm component. Latex gloves are effective in containing bac- skin scales, and other particles shed by the most scrupu- scrubbed hands. However, the outer sterile surfaces do main sterile since they will contact the room air, sanitized items, work counters, and other surfaces that, while clean, ot sterile. Therefore, operators must perform aseptic ma- ations in a manner designed to prevent touching critical sites he gloved fingers or hands. Further, operators should at- to maintain gloved hand surfaces as free from contami- as possible by repeated rinsing with a sterile sanitizing ch as IPA, during use.

ue latex gloves must be worn when operator protection as s product protection is essential, such as during operations ng cytotoxic or otherwise hazardous sterile products.

oper scrubbing and gowning immediately prior to entry into uffer Room is required of all personnel, without exception. the operator find it necessary to leave the room, the coat arefully removed at the entrance and hung inside out gowning upon re-entry, but only during the same shift. How- air covers, masks, shoe covers, and gloves should be dis- d and new ones donned prior to re-entry.

high-risk operations, it is especially critical to minimize sk of contamination on lab coats, coveralls, and other garb worn in the Buffer Room. Preferably, fresh clean garb d be donned upon each entry into the Buffer Room to avoid ting contaminants from previously worn garb. Alterna- garb that has been worn may be removed with the intention arbing for re-entry into the Buffer Room and stored during terim under proper control and protection in the Anteroom. worn or taken outside the confines of the Anteroom should worn in the Buffer Room.

spersion of particles from body surfaces, such as from skin sunburn, or cosmetics, increases the risk of contamination tical sites and should be appropriately controlled or mini- If severe, the operator should be excluded from the Buffer until the condition is remedied, especially for high-risk tions.

Suggested Standard Operating Procedures (SOPs)

The pharmacy should have written, properly approved SOPs designed to ensure the quality of the environment in which an HSD is prepared. The following procedures are recommended:

(1) Access to the Buffer Room should be restricted to qualified personnel with specific responsibilities or assigned tasks in the area.

(2) All cartoned supplies should be decontaminated in the Anteroom by removing them from shipping cartons and wiping with a disinfecting agent, such as sterile IPA, while being transferred to a clean, sanitized cart or other conveyance for introduction into the Buffer Room. Individual pouched supplies need not be wiped because the pouches can be removed as these supplies are introduced into the Buffer Room.

(3) Supplies required frequently or otherwise needed close at hand but not necessarily needed for the scheduled operations of the shift should be decontaminated and stored on the shelving in the Anteroom.

(4) Carts used to bring supplies from the storeroom should not be rolled beyond the demarcation line in the Anteroom, and carts used in the Buffer Room should not be rolled outward beyond the demarcation line unless cleaned and sanitized before returning.

(5) Generally, supplies required for the scheduled operations of the shift should be prepared and brought into the Buffer Room, preferably on one or more movable carts. Supplies that are required for back-up or general support of operations may be stored on the designated shelving in the Buffer Room, but excessive accumulation of supplies should be avoided.

(6) Objects that shed particles should not be brought into the Buffer Room, including pencils, cardboard cartons, paper towels, and cotton items.

(7) Traffic flow into and out of the Buffer Room should be minimized.

(8) All personnel preparing to enter the Buffer Room should remove all jewelry from hands and arms.

(9) All personnel entering the Buffer Room should first scrub hands and arms with soap, including using a scrub brush on the fingers and nails. An air dryer or disposable nonshedding towels should be used to dry hands and arms after washing.

(10) All personnel entering the Buffer Room, after scrubbing, should don attire as described under *Personnel and Gowning*.

(11) No chewing gum, candy, or food items may be brought into the Buffer Room.

(12) At the beginning of each shift and when spillage occurs, the LAFW surface should be wiped with a clean, nonlinting wiper or sponge dampened with distilled water. The entire inside of the LAFW should then be wiped with another clean wiper wet with an approved disinfectant, such as IPA.

(13) The blower of the LAFW should be operated continuously. However, in the event of a long period of nonuse, the blower may be turned off and the opening covered with a plastic curtain or other shield. Before reuse, all internal surfaces should be sanitized and the blower operated for a minimum of 30 minutes.

(14) Traffic in the area of the LAFW should be minimized and controlled. The LAFW should be shielded from all less clean air currents that are of higher velocity than the clean laminar airflow.

(15) Supplies to be utilized in the LAFW for the planned procedures should be accumulated and then decontaminated by wiping the outer surface with IPA or removing the outer wrap at the edge of the LAFW as the item is introduced into the aseptic work area.

(16) After proper introduction into the LAFW of supply items required for and limited to the assigned operations, they should be so arranged that a clear, uninterrupted path of HEPA-filtered air will bathe all critical sites at all times during the planned procedures. That is, no objects may be placed behind an exposed critical site in a horizontal position or above in the vertical laminar flow workbench.

(17) All supply items should be arranged in the LAFW to reduce clutter and to provide maximum efficiency and order for the flow of work.
(18) All procedures should be performed in a manner designed to minimize the risk of touch contamination. Gloves should be sanitized with adequate frequency.
(19) All rubber stoppers of vials and bottles and the neck of ampuls should be sanitized with IPA prior to the introduction of a needle or spike for the removal of product.
(20) After the preparation of every admixture, the contents of the container should be thoroughly mixed and then inspected for the presence of particulate matter, evidence of incompatibility, or other defects.
(21) After procedures are completed, used syringes, bottles, vials, and other supplies should be removed, but with a minimum of exit and re-entry into the LAFW to minimize the risk of dragging contamination into the aseptic workspace.

Environmental Control and Monitoring Program

Because achieving or maintaining sterility is essential in the preparation of sterile products, the assessment of the level of control of the environment in which those products are prepared is recommended. The level of environmental control achieved may be evaluated by measuring the viable and the total (viable and nonviable) number of particles in the environment. Viable particle counting is recommended for environmental assessment in conjunction with the preparation of an HSD. Total particle counting is recommended for facility classification.

Viable particle counts are indicative of the portion of the total particle counts that represent microorganisms, normally reported as Colony Forming Units (cfu's), since typical viable particle counting results do not distinguish between single microorganisms and clusters. The difficulties in obtaining consistent and quantitative growth of microorganisms and the time lag between sampling and obtaining results because of growth time are important environmental monitoring limitations.

Total particle counts are usually performed by means of electronic instruments that give results instantly, based upon the measurement of particles in a prescribed volume of air. Clean room classifications (see Table 2) are based upon such measurements. A number of different types of instruments are available. Measurements can be made one at a time, or, with most instruments, automatically obtained on a planned, ongoing schedule. Instantaneous results permit assessment of environmental particulates at any given time and permit rapid changes in the control program should the results indicate a problem. However, these results do not distinguish between viable and nonviable particulates.

This section focuses on the measurement and monitoring of programs for viable particles.[5]

TESTING PROGRAM

A testing program is based upon the use of various methods for collecting an environmental sample on a nutrient, usually solid, culture medium, incubating at a temperature and for a time period conducive to the multiplication of any collected microorganisms, and then counting the discrete colonies that have developed on the surface of the medium. The count, reported as cfu's, is a measure of microbial contamination of the environment at the time and under the conditions of sampling. For more details, see *Microbiological Evaluation and Classification of Clean Rooms and Clean Zones* ⟨1116⟩.

In general, test methods for airborne environmental microbial contaminants either determine the number of cfu's collected in a measured volume of air ("quantitative" or "volumetric") or during a specified period of time. Any test method sensitive enough to show trends in environmental quality under specified conditions of the sampling used is acceptable. In general, quantitative methods are preferred over nonquantitative methods. When using either approach, the sample size should be sufficient to give a result of statistical significance. The testing program should also include surface sampling.

[5] The PDA Technical Report No. 13, 1990, may be consulted for details and monitoring methods not covered in this section.

Dynamic monitoring, that is, testing under operating conditions during work activity, should be used routinely in order to get a cfu count during the processing of an HSD that demonstrates the critical effects of the presence and movement of operators. The latter is possible when comparing results from dynamic monitoring with results from static monitoring when no processing is being performed. Static monitoring generally evaluates the status of the facilities, operating equipment, and housekeeping.

The greatest value of ongoing microbial monitoring is achieved when microbial recoveries show trends. For a given environmental area, a baseline count is determined under the best environmental control believed to be possible for the area. Sampling should be done in selected locations and in a manner intended to reflect best the environmental conditions in the area. The encircled letters on Figure 1 illustrate possible sampling locations. To establish the baseline count, a large number of samples should be taken in multiple locations over a period of time to reflect time of day and week, workload conditions, and, preferably, personal variations. Analysis of these results would give counts normally expected to be achievable and the identification of a reduced number of selected sites expected to reflect the environmental conditions in the area with subsequent monitoring. This analysis then becomes the basis for ongoing monitoring. The baseline count limits may be slightly higher for low-risk operations than for high-risk operations. Subsequently, any significant change in the counts obtained, either as a single spike or a gradual rise in the cfu count, would require investigation into the cause.

When counts exceed the established baseline count by a determined amount (the action level), a written plan of action should be initiated. The plan would usually call for a repeat of the monitoring tests the next day and an investigation into the cause, and may include such actions as review of decontamination procedures, resanitization of the LAFW and the Buffer Room, change to a different sanitizing agent, or retraining of operators. It should be remembered that microbial monitoring results are not available until after incubation, usually 48 hours, thus causing a delay in taking any corrective action. Therefore, trends should be detected as early as possible. Action levels would be slightly higher for low-risk operations than for high-risk operations.

The workspace in an LAFW is the only environment required to meet Class 100 (MCB-1) conditions, with the exception of specialized rooms (e.g., laminar flow rooms) specifically designed to achieve Class 100 conditions. To ensure that Class 100 conditions are met continuously, the LAFW (or room) should be certified after installation and recertified at least annually and after the unit is moved. This certification process includes testing for HEPA filter leaks and the laminar airflow velocity. The microbial counts normally anticipated within the LAFW (or room) will average less than one per 10 cubic feet, even under dynamic testing conditions. However, culture media exposed to the air stream tends to dry and, therefore, should not be exposed for more than one hour. Table 3 provides examples of microbial environmental test limits, and is presented as a guide.[6]

TEST METHODS

A well-known test method is the exposure of settling plates, that is, petri dishes with solid nutrient agar medium contained in the bottom section of the plate. These 100-mm diameter plates are simply opened and allowed to rest on a surface for a specified period of time. They do not sample a known volume of air. The viable particles collect on the agar surface as they fall from the environment or are impacted by the movement of air or people. Three-hour exposure of settling plates in a room is an appropriate, easy, and inexpensive way to obtain a representation of the contamination that could be expected to settle from the air at the sampling site.

Well-known volume-of-air samplers include the slit-to-agar (STA) sampler and the Reuter centrifugal air sampler (RCS). The STA sampler utilizes a revolving nutrient agar plate under a slit orifice to impinge the air sample particles on the surface of the nutrient agar in the plate. While the unit is portable, it requires a vacuum and an electrical source. The unit

[6] These test limits were compiled from suggested values in Technical Monograph No. 2, the Parenteral Society (Great Britain), 1989, and other sources. They were also correlated with the USP proposed data in *Microbiological Evaluation and Classification of Clean Rooms and Clean Zones* ⟨1116⟩.

ilized but not sterilized. The RCS draws air with an impeller the head of the unit and centrifugally impacts any particles nutrient agar strip around the perimeter of the head. The samples in multiples of 40 liters per minute and is sanitizable portable, with a self-contained battery power unit. Both of e units are relatively expensive but, unlike settling plates, the advantage of quantitative sampling.

urface sampling is most frequently done with contact plates[7] etect accumulated microbial contamination on a flat surface. e plates are 60 mm in diameter and filled with nutrient agar ium to form a convex surface. The agar usually contains ives to help neutralize residues of disinfectants that may be e test surface. The agar is pressed onto a flat surface lifting microorganisms present onto the surface of the agar. This od can be considered to be relatively quantitative when conants are residing superficially on a flat, smooth surface. ever, residual agar must be thoroughly removed from the urface.

AN EXAMPLE OF AN ENVIRONMENTAL MONITORING PROGRAM

e following is a suggestion for one possible environmental toring program consisting of multiple tests to determine the ine count and subsequent reduced testing for ongoing mong of the environmental control conditions.[8]

ing plates should be uncovered at sites A–N (see Fig. 1) posed for 3 hours (except 1 hour at site "A"), both under and dynamic conditions. This test should be repeated each nd each shift for at least one week, preferably two weeks. A or RCS air samplers are used, at least 10 cu. ft. (280 air samples should be taken at sites B, D, E, J, K, and L. utrient agar plates or strips are then incubated at 30° to or 48 hours and the colonies counted. These tests should peated about six months later. The average number of colat each site is computed to give baseline counts, being sure ousekeeping and other environmental control procedures nctioning at maximum efficiency.

ilarly, at the end of each shift and before any clean-up zation is done, perform surface sampling with contact plates same sites, being careful to remove any residual medium the surfaces with an alcohol wipe. In addition, at least the finger of each operator should be rolled on a contact plate. results of these evaluations are critically reviewed. Using ta given in Table 3 as an example, a reduced number of

Table 3. A Sample Dynamic Environmental Microbial Monitoring Program.

Site	Baseline cfu	Low-risk Action Level	High-risk Action Level
ttling Plates*			
A	0,1	3	2
D	2,3	6	4
E	4,5	10	6
J	5	10	7
L	8	15	10
ontact Plates			
D	2,3	6	4
E	4,6	10	7
J	6	12	8
L	8	15	10
A or Impaction Sampler**			
A	0,1	3	2
E	5	10	7
H	8	15	10

Based on 3-hour exposure, except 1-hour for "A." See 1 for site locations.
Based on 10 cu. ft. samples.

hes meeting these specifications are obtainable from lab- supply houses as Rodac brand, or use the equivalent. e also *Am. J. Hosp. Pharm.* 1980; 37:668.

sites for monitoring, which give the best evidence of the level of microbial control maintained during facility operation, can be selected. Monitoring tests under dynamic conditions should then be performed at least weekly during the shift of highest activity at the selected sites (i.e., sites D, E, J, and L, or other sites that give evidence of being more representative of the true environmental control conditions). At least monthly another shift should be monitored in the same manner. Volume-of-air samples might be reduced to one site in each room weekly. However, the number of monitoring sites or the sampling frequency should be increased if there is any indication that the monitoring program is inadequate. Action levels are determined by making a reasoned judgment. A 50% increase above the baseline count is probably reasonable for high-risk operations. For low-risk operations an increase of 100% probably would be acceptable. However, whenever a rising trend appears to be in progress, the operations should be closely monitored with more frequent sampling being performed to confirm whether or not a trend is occurring.

PROCESSING

Personnel Training and Evaluation

The pharmacy should follow a written program of training and performance evaluation designed to ensure that each person working in the aseptic area has the appropriate knowledge and skills necessary to perform the assigned tasks properly. Each person assigned to the aseptic area must successfully complete specialized training in aseptic technique and aseptic area practices.

Training should include didactic material and practical skills activities. Evaluation should include written testing and a written protocol of frequent routine performance checks involving random direct observation of critical operations and adherence to all aseptic area procedures and codes. Prompt appropriate action should occur to correct performance deviations, whether detected during a performance check or informally. At six-month intervals each person's continuing training needs should be reassessed, then documented, to ensure that skill levels are maintained.

Aseptic Technique

All critical operations are carried out by appropriately trained and qualified personnel in an LAFW using proper aseptic technique described in a written procedure (see the section *Suggested Standard Operating Procedures*). Aseptic technique is equally applicable to the preparation of sterile sensitizing and chemotoxic agents. However, it should be recognized that additional precautions must be used to protect the compounder and the compounding environment from the adverse effects of the agents being processed. A vertical laminar flow workbench (VLFW) with biohazard control capabilities, the protective capabilities of garb and gloves, sprayback and spill control techniques, the use of specialized compounding devices, and proper disposal are some of the additional measures to be considered.

Components

The pharmacy should follow written procedures to ensure that all items used to compound sterile drug products retain their purported or expected qualities at the time of use.

STERILE COMPONENTS

Commercially available sterile drug products, sterile ready-to-use containers and devices are examples of sterile components. A written procedure for unit-by-unit physical inspection preparatory to use should be followed to ensure that these components are sterile, free from defects, and otherwise suitable for their intended use.

NONSTERILE COMPONENTS

Drug components should meet compendial standards. Certificates of analysis from reputable manufacturers of bulk drug substances may be used to establish that each lot of bulk drug substance received by the pharmacy meets its specifications. Bulk drug substances stored properly in the pharmacy can be expected to retain their quality until the manufacturer's labeled expiration date. Bulk drug substances that are not labeled with a manufacturer's expiration date should be dated upon receipt, stored

properly, dated when opening the container, used within a reasonable period of time, and visually inspected by the pharmacist upon use. The conditions under which containers of bulk drug substances are opened and the technique of the contents' withdrawal should be strictly controlled. Additionally, the devices used to withdraw the contents should be clean to preclude contamination of the remaining contents. The pharmacy may repackage bulk drug substances into smaller, suitable, and properly sealed containers (e.g., using a shrink seal) to minimize the risk of contamination. Upon receipt of each lot of bulk drug substance used to compound an HSD, the pharmacy should perform an inspection of the lot for any visual evidence of deterioration, other types of unacceptable quality, and wrong identity. Visual inspection of bulk drug substances should be performed routinely.

Because finished compounded HSDs are not usually tested for pyrogens, nonsterile bulk drug substances could impart pyrogenic properties to the finished product. Therefore, the pharmacy should have a procedure to ensure that the final product does not exceed specified endotoxin limits. See *Bacterial Endotoxins Test* ⟨85⟩ for procedural details concerning endotoxin testing.

Equipment

The pharmacy should ensure that equipment, apparatus, and devices used to compound an HSD are capable of consistently operating properly and within acceptable tolerance limits. Written procedures should be established and followed that include equipment calibration, annual maintenance, monitoring, and control. Routine maintenance checks should be documented. Personnel should be qualified through an appropriate combination of specific training and experience to operate or manipulate any item of equipment, apparatus, or device to which they will be assigned to use when preparing drug products for patients. Training should include the ability to determine whether any item of equipment is operating properly or is malfunctioning.

FINISHED PRODUCT RELEASE CHECKS AND TESTS

All HSDs should be subjected to appropriate checks or tests to ensure that only those HSDs free from defects and meeting all quality specifications will be distributed. An HSD should not be released until all quality specifications have been reviewed and it is determined that all release requirements are met.

Physical Inspection

All finished HSDs should be individually inspected in accordance with written procedures after compounding and, if not distributed promptly, prior to leaving the pharmacy. Immediately after compounding and as a condition of release, each product unit, where possible, should be inspected against lighted white and black backgrounds for evidence of visible particulates or other foreign matter. Pre-release inspection should also include container-closure integrity and any other apparent visual defect. Products with observed defects should be immediately discarded or marked and segregated from acceptable products in a manner that prevents their administration to patients. When products are not distributed promptly after preparation, a predistribution inspection should be conducted to ensure that an HSD with defects, such as precipitation, cloudiness, and leakage, which may develop between the time of release and the time of distribution, is not released.

Compounding Accuracy Checks

Written procedures for double checking compounding accuracy should be followed for every HSD prior to release. The double check system should meet state regulations and include label accuracy and accuracy of the addition of all drug products or ingredients used to prepare the finished product and their volumes or quantities. The used additive containers and, for those additives for which the entire container was not expended, the syringes used to measure the additive, should be quarantined with the final products until the final product check is completed. Syringe plungers should be drawn back to the volume mark used for each additive, if the additive volume was not checked prior to the addition. Automated pump settings should be verified just prior to or just after pumping and mixing. In addition, the volumes of each ingredient actually pumped should be checked to establish that the accuracy of the automated pump is within limits set by the manufacturer. Written procedures for accountability of all drug product units used in the preparation of HSDs should be followed.

Additional finished product tests should be performed on *high-risk HSDs*, as follows.

Sterility Testing

Sterility testing should be performed on *Category II* high-risk HSDs promptly upon the completion of preparation. The sterility test, including the sampling scheme, should be conducted according to one of the USP methods (see *Sterility* ⟨71⟩). Membrane filtration is the method of choice where feasible. A method not described in the USP may be used if validation results demonstrate that the alternative is at least as effective and reliable as the USP membrane filtration method or the direct inoculation method where the membrane filtration method is not feasible.

Normally, the HSD should not be released for patient use until test results show no evidence of microbial contamination of the product. However, when the HSD must be released on the same day of compounding prior to the completion of the sterility testing, the HSD can be conditionally released. In such a case, the pharmacy should have a procedure requiring daily observation of the media and requiring an immediate recall if there is any evidence of microbial growth. In addition, the physicians of those patients to whom a potentially contaminated HSD was administered should be notified as to the potential risk to the patient. Positive sterility test results should prompt an investigation of aseptic technique, environmental control, and other sterility assurance controls to identify and correct problems as quickly as possible.

Pyrogen Testing

Each HSD prepared from nonsterile drug components or from an intermediate compounded for a nonsterile component should be tested for pyrogen or endotoxin according to the recommended methods (see *Bacterial Endotoxins Test* ⟨85⟩). The product should not be released until it has been determined that the endotoxin limit specified for the product is not exceeded.

Potency Testing

The pharmacy should have a procedure for a pre-release check of the potency of the active ingredients in HSDs prepared from nonsterile bulk active ingredients. The procedure should include at least the following verifications by a pharmacist:

(1) The lot of the active ingredient used for compounding has the necessary identity, potency, purity, and other relevant qualities. For example, this can be established for official drug substances by comparing the information stated on the lot's certificate of analysis with the requirements specified in the USP monograph for the substance.

(2) All weighings, volumetric measurements, and additions of ingredients were carried out properly. This can be established by reviewing compounding records to ensure that these steps were confirmed and initialed by a second person during compounding.

(3) The compounding or control records include documentation that the fill volumes of all units available for use were checked and were correct.

(4) The final yield is confirmed to be consistent with the theoretical yield.

In addition, instrumental analysis of potency should be performed to support expiration dating periods greater than those assigned to HSDs prepared from nonsterile drug substances.

STORAGE AND EXPIRATION DATING

Each finished drug product unit should bear labeling that identifies the product's storage requirements and expiration date and, where appropriate, the time of day beyond which the product is not to be used. Unless otherwise indicated, HSDs should be refrigerated until time of use, with allowance for adequate time to equilibrate to room temperature before administering.

ent. HSDs intended for administration promptly after com-ding may be retained at room temperature from the time of pounding.

ven under the best of conditions, there is always the likelihood unsuspected microorganisms might inadvertently gain entry the HSD during aseptic processing. Thus, as an adjunct lity assurance measure, HSDs not intended for prompt use ld be stored at a temperature no greater than 4°, that is, at mperature expected to inhibit microbial growth. The multi-HSDs (injections prepared for administration by a portable ion pump or reservoir) should be started promptly after prep-on, and administration should be completed within 7 days. e HSDs, such as 5-fluorouracil, that cannot be refrigerated preparation should be used within 28 hours of preparation rther assurance of sterility.

harmacists should also consider the effect of "cumulative" temperature storage on the physical-chemical stability and acteristics of the HSD. For example, an HSD may be re-d from the refrigerator and allowed to equilibrate to room rature, only to be replaced into the refrigerator. This could any number of times before the product is ultimately by the patient. Thus, the original expiration date assigned e pharmacist could easily be invalidated under these cir-tances. A procedure should be in place that details what is done when this situation occurs. Should this situation arise, harmacist needs to determine what the actual stability of duct will be, keeping in mind the cumulative effects of nperature storage upon the product. The drug product's facturer or other credible stability reference source should sulted, particularly for expensive biotechnology or chem-peutic drugs.

ditionally, some HSDs may be subjected to elevated tem-re conditions, (e.g., body temperature) for continuous or drug delivery devices such as ambulatory infusion pumps, table infusion devices, and elastomeric infusion devices. macists should have adequate stability reference data to en-hat the product's potency characteristics are maintained stored at these elevated temperatures during the labeled of time chosen. HSDs may be frozen if adequate stability ce to support freezing is available.

light-sensitive products should be suitably protected from from the time of preparation until the time of use or, where ted, until the conclusion of administration.

Determining Expiration Dates

re possible, the expiration date should be in accordance llowances specified in the approved labeling. However, e, published stability information is sometimes lacking for pes of drugs. In these instances, pharmacists should con-the drug's manufacturer to establish an expiration date. se of compelling patient-care needs, a pharmacist may be to stay within the approved labeling and product guide-tated in the package insert. For example, a higher con-ion of drug may be prescribed; different diluent, container, ay be necessary; or the patient may require the HSD for eriods of time. The pharmacist should communicate the ons from the package insert to the manufacturer when ting stability information. Otherwise, the pharmacist should that the manufacturer's stability information is product e, that is, the exact strength, diluent, fill volume, and con-type (PVC bag, plastic syringe, elastomeric infusion device, ill be used by the pharmacist when preparing the HSD. macists should obtain a letter from the manufacturer cer-the expiration dating period provided. Information pro-by the manufacturer is usually for the HSD's chemical and al stability only and would therefore not be relevant to assurance imparted by the pharmacist each time the is made. Therefore, it is the pharmacist's responsibility re that compounding methods are validated to ensure final sterility. Expiration dating not specifically referenced in oduct's approved labeling should be limited to 30 days.

nsure consistent practices in determining and assigning ion dates, the pharmacy should have written policies and ures governing the determination of the expiration dates of its compounded products. The following information helpful in providing a basis for these policies and pro-s.

Product-specific, experimentally determined stability data based on sound stability evaluation protocols are preferable to published stability information for the prediction of expiration dates. Pharmacists should consult the general information chapter *Pharmaceutical Dosage Forms* ⟨1151⟩ for the appropriate stability parameters to be considered when initiating or evaluating a product-specific stability study. However, the use of professional judgment based on accumulated information may also be acceptable for determining expiration dates.

It should be recognized that the only truly valid evidence of stability for predicting expiration dating is from product-specific (appropriate bracketing is acceptable) experimental studies. Predictions based on other evidence, such as publications, charts, tables, etc., would result in theoretical expiration dates. Theoretically predicted expiration dating introduces varying degrees of assumptions and hence a likelihood of error, or at least inaccuracy. The degree of error or inaccuracy would be dependent upon the extent of differences between the HSD's characteristics (e.g., composition, concentration of ingredients, fill volume, container type and material, etc.) and the characteristics of the products from which stability data or information are to be extrapolated. Thus, the greater the doubt of the accuracy of theoretically predicted expiration dating, the greater the need to determine dating periods experimentally. Theoretically predicted expiration dating periods should be seriously considered for HSDs prepared from nonsterile bulk active ingredients having therapeutic activity, especially where these HSDs are expected to be compounded routinely. Semi-quantitative procedures, such as thin-layer chromatography (TLC), may be acceptable for many HSDs. However, quantitative stability-indicating assays, such as high-performance liquid chromatography (HPLC), would be more appropriate for certain critical HSDs. Examples include HSDs with a narrow therapeutic dosage range or a narrow therapeutic index where close monitoring or titering is required to ensure therapeutic effectiveness or to avoid toxicity; where a theoretically established expiration dating period is supported by only marginal evidence; or where a significant margin of safety cannot be verified for the proposed theoretical expiration dating period.

Additionally, conditions to which the finished product may be subjected during in-home use (e.g., in homes without air-conditioning in a hot climate) should be considered on a patient-by-patient basis. Thus, the possible need to shorten a general expiration date should be considered at the time of dispensing based on the particular circumstances of the patient.

In all instances where alternate informational resources are used to establish an expiration date for a drug product, the pharmacist should ensure that those resources have undergone critical evaluation in conjunction with the specific product for which an expiration date is established. Expiration dates predicted from alternate informational resources should be conservative and not extend beyond the realistic and practical patient care needs of the pharmacy. Pharmacists should subsequently maintain a record of the specific basis used to establish the expiration date for each compounded drug product. Pharmacists should utilize an exception log for products with expiration dates that fall outside of the pharmacy's established SOPs on stability and expiration dating. Alternatively, the exceptional reasons for changing the product's expiration date may also be documented in the patient's chart.

Monitoring Controlled Storage Areas

To ensure that product potency is retained through the expiration date, pharmacists must monitor the drug storage areas within the pharmacy. Controlled temperature storage areas in the pharmacy (refrigerators, 2° to 8°, freezers, −20° to −10°, and incubators, 30° to 35°, etc.) should be monitored at least once daily and the results documented on a temperature log. Additionally, pharmacy personnel should note the storage temperature when placing the product into or removing the product from the storage unit in order to monitor for any temperature aberrations. Suitable temperature recording devices may include a calibrated continuous recording device or an NBS calibrated thermometer that has adequate accuracy and sensitivity for the intended purpose and should be properly calibrated at suitable intervals. If the pharmacy uses a continuous temperature recording device, pharmacy personnel should verify at least once daily that the recording device itself is functioning properly.

The temperature sensing mechanism should be suitably placed in the controlled temperature storage space to reflect accurately its true temperature. In addition, the pharmacy should adhere to appropriate procedures of all controlled storage spaces to ensure that such spaces are not subject to significantly prolonged temperature fluctuations as may occur, for example, by leaving a refrigerator door open too long.

MAINTAINING PRODUCT QUALITY AND CONTROL AFTER IT LEAVES THE PHARMACY

Packing

The pharmacy is responsible for ensuring that the HSDs are suitably packed for transport. Packing should provide adequate control of the conditions under which HSDs are transported to the patient. Packing specifications, including configuration and materials, should be appropriate, as determined on a product-by-product basis, to maintain the storage conditions necessary to protect the product against adverse physical conditions such as temperatures beyond the range allowable for the HSD and, where indicated, exposure to light. Packing should retain adequate effectiveness for the duration of, and under the environmental conditions expected during, transit.

In-transit temperatures of HSDs should be maintained near the midpoint of the HSDs' specified upper and lower limits, recognizing that some temperature excursion, not to exceed the product's specified limits, is permissible during transit. Under no circumstances may excursions exceed the limits specified in the *General Notices* under *Storage Temperatures* for the defined temperature conditions.

The pharmacy should have and follow written procedures that specify packing techniques, configurations, and materials for groups of products with common storage characteristics and for specific products where unique storage conditions are required to retain adequate stability and product quality. It must be recognized that additional precautions should be used to protect the shipper, patient, and caregiver from adverse effects from any leakage of sensitizing or chemotoxic agents. Although written procedures should also ensure that biohazard controls are adequate for transit conditions and for meeting all OSHA and local requirements, this topic is beyond the scope of this chapter, and other references should be consulted.

The pharmacy should ensure that transit specifications and procedures are effective. For example, post-transit determinations of internal pack temperatures following several trial shipments of goods packed with new or modified materials, configurations, or techniques provide an indicator of packing suitability under actual transit conditions. Following the initial determination of packing suitability, occasional shipments should be subsequently checked, especially whenever transit conditions vary, such as from seasonal temperature changes or transit times. Because different packing configurations, pack size, internal packing matrices (e.g., insulated coolers or containers, styrofoam, bubble wrap, freezer packs, etc.) and pack thickness differ in their resistance to heat penetration or loss, packing should not vary from established procedures and specifications without evaluation.

Transit

Unlike the selection of the adherence to packing specifications, the pharmacy may lack complete control over transit time and conditions. However, the pharmacy can establish reasonable expectations of transit time and conditions and can carry out procedures to ensure that expectations are usually met. The determination of packing suitability is based on these expectations. Where possible, delivery personnel should be trained by the pharmacist on how to transport HSDs.

When common carriers are utilized, the pharmacy is responsible for choosing a reliable carrier capable of consistently fulfilling the pharmacy's requirements for delivery schedules, transit time duration, handling, care, external temperature controls, and special handling that may be required. The pharmacy should provide the carrier with a written statement of shipping requirements and should obtain from the carrier an assurance of capability and commitment for fulfilling these requirements before the pharmacy engages the carrier's services.

Delivery personnel, whether employees of the pharmacy, the parent organization, or the common carrier, should know the shipping requirements of each package consigned. Printed labels prominently displayed on the exterior of each package, are usually sufficient. Supplementary printed instructions may be necessary in some instances.

The pharmacy should have an effective system for the routine evaluation of shipping performance. For example, the pharmacy might periodically review delivery receipts or conduct periodic shipment follow-ups by telephoning patients or caregivers to verify time, internal temperature (temperature indicators such as strips or probes inside packages provide objective evidence for determining the adequacy of temperature control), condition of goods upon receipt, and courteousness of personnel are some determinants of acceptable shipping performance.

In The Home

The pharmacy's basic responsibilities for ensuring that HSDs in the home maintain their quality until administered include the following:

(1) The immediate labeling of the HSD container displays prominently and understandably the requirements for proper storage and expiration dating.

(2) Adequate information is obtained to assure the pharmacist that the storage conditions existing in the home are suitable for the HSD's specified storage requirements. (It is acceptable for the pharmacist to obtain this information through documentation by nursing or delivery personnel.)

(3) The patient has an acceptable temperature measurement device in the refrigerator and understands the importance of its use for maintaining proper storage temperatures.

(4) A separate information sheet is issued and includes instructions for proper storage, interpretation of the expiration dating, and how to look for signs of unsuitability for use.

The patient or caregiver should be informed of the need to notify the pharmacy promptly of any actual or suspected malfunction of the refrigerator, freezer, or temperature measurement device. The pharmacy should assist patients or caregivers as necessary to ensure that proper storage conditions for HSDs are maintained with little or no interruption.

The pharmacy is responsible for ensuring that the home is visited at regular intervals to confirm compliance with appropriate drug storage conditions, cleanliness, separation of food and drug items, avoidance of improper re-use of multiple dose containers or supplies such as tubing or syringes, avoidance of use of single-dose products as multiple-dose containers, and product inventory as indicative of product usage compliance. Improperly stored, exteriorly soiled, expired, or visibly defective drug products should be removed from the patient's possession using the opportunity to instruct the patient or caregiver to reinforce storage and handling responsibilities. Similarly, the home visit should also assess compliance with waste containment and disposal. The pharmacy may entrust the home visit to another health professional or paraprofessional.

PATIENT OR CAREGIVER TRAINING

A formal training program should be provided as a means to ensure understanding and compliance with the many specific and complex responsibilities placed upon the patient or caregiver for the storage, handling, and administration of HSDs. The educational objectives for the training program should include all patient care responsibilities expected of the patient or caregiver and should be specified in terms of patient or caregiver competencies.

Upon the conclusion of the training program, the patient or caregiver should, correctly and consistently, be able to do the following:

(1) Describe the therapy involved, including the disease condition for which the HSD is prescribed, goals of therapy, expected therapeutic outcome, and potential side effects of the HSD.

(2) Inspect all drug products, devices, equipment, and supplies on receipt to ensure that proper temperatures were maintained during transport and that goods received show no evidence of deterioration or defects.

) Handle, store, and monitor all drug products and related supplies and equipment in the home, including all special requirements related to same.
Visually inspect all drug products, devices, and other items the patient or caregiver is required to use immediately prior to administration in a manner to ensure that all items are acceptable for use. For example, HSDs should be free from leakage, container cracks, particulates, precipitate, haziness, discoloration, or other deviations from the normal expected appearance, and the immediate packages of sterile devices should be completely sealed with no evidence of loss of package integrity.
Check labels immediately prior to administration to ensure the right drug, dose, patient, and time of administration.
Clean the in-home preparation area, scrub hands, use proper aseptic technique, and manipulate all containers, equipment, apparatus, devices, and supplies used in conjunction with administration.
Employ all techniques and precautions associated with HSD administration, for example, preparing supplies and equipment, handling of devices, priming the tubing, and discontinuing an infusion.
Care for catheters, change dressings, and maintain site patency as indicated.
Monitor for and detect occurrences of therapeutic complications such as infection, phlebitis, electrolyte imbalance, and catheter misplacement.
Respond immediately to emergency or critical situations such as catheter breakage or displacement, tubing disconnection, clot formation, flow blockage, and equipment malfunction.
Know when to seek and how to obtain professional emergency services or professional advice.
Handle, contain, and dispose of wastes, such as needles, syringes, devices, biohazardous spills or residuals, and infectious substances.
ning programs should include hands-on demonstration and e with actual items that the patient or caregiver is expected such as HSD containers, devices, and equipment. The or caregiver should practice aseptic and injection techunder the direct observation of a health professional.
pharmacy is responsible for ensuring initially and on an g basis that the patient or caregiver understands, has mastand is capable of and willing to comply with all of these care responsibilities. This should be achieved through a written assessment program. All specified competencies patient or caregiver's training program should be formally d. The patient or caregiver should be expected to dem- to appropriate health care personnel their mastery of signed activities before being allowed to administer HSDs vised by a health professional.
ed material such as checklists or instructions provided training may serve as continuing post-training reinforcer learning or as reminders of specific patient or caregiver ibilities. Post-training verbal counseling should also be eriodically, as appropriate, to reinforce training and to ontinuing correct and complete fulfillment of responsi-

TIENT MONITORING AND COMPLAINT SYSTEM

pharmacy must have written policies and procedures de- the monitoring of patients using HSDs and the handling rts of adverse events.

Outcome Monitoring

pharmacy is responsible for developing a patient monilan, which includes written outcome measures and sysr routine patient assessment. The outcome monitoring should provide information suitable for the evaluation of lity of patient care and of pharmaceutical services. Exof assessment parameters include infection rates, rehosion rates, incidence of adverse drug reactions, catheter ations, and other variables that may serve as meaningful rs of the effectiveness and suitability of the home use of HSDs. In selecting suitable outcome measures, the focus should be on high-risk, high-volume, or problem-prone factors.

Reports

The pharmacy should have policies and procedures for the receipt, documentation, handling, and disposition of reports of patient problems, complaints, adverse drug reactions, drug product or device defects, and other adverse events reported by patients, caregivers, family members, pharmacists, or other health professionals. The pharmacy should have a procedure to ensure that the patient receives prompt and appropriate medical attention as necessary in response to all adverse incidents from HSDs or devices. When a complaint or problem prompts a suspicion that an HSD or a device may be defective, the pharmacy should also be able to identify and recall the potentially defective item to the patient level whenever appropriate.

Procedures should also include a mechanism for periodic review of reports received to determine any need for correction of underlying systems problems. All reports received should be maintained in a log, file, or binder dedicated for this purpose and readily retrievable as needed for subsequent analysis, legal or regulatory inquiry, or quality assurance audit. Standardized forms or formats for the reporting and recording of incidents, complaints, etc., should be used. Reports should be completed and signed by the individual receiving it or by the individual involved in the situation. Procedures should depict the classification, documentation, investigation, and resolution of all reports and should provide a mechanism for participation in various federal and state reporting programs such as USP or FDA programs for reporting reaction problems, or defects with drug products or medical devices.

THE QUALITY ASSURANCE PROGRAM

A provider of HSDs should have in place a formal Quality Assurance (QA) Program[9] intended to provide a mechanism for monitoring, evaluating, correcting, and improving the activities and processes described in this chapter. Emphasis in the QA Program should be placed on maintaining and improving the quality of systems and the provision of patient care. In addition, the QA program should ensure that any plan aimed at correcting identified problems also includes appropriate follow-up to make certain that effective corrective actions were performed.[10]

Characteristics of a QA plan include the following:
(1) Formalization in writing;
(2) Consideration of all aspects of the preparation and dispensing of products as described in this chapter, including environmental testing, validation results, etc.;
(3) Description of specific monitoring and evaluation activities;
(4) Specification of how results are to be reported and evaluated;
(5) Identification of appropriate follow-up mechanisms when action limits or thresholds are exceeded; and
(6) Delineation of the individuals responsible for each aspect of the QA program.

In developing a specific plan, focus should be on establishing objective, measurable indicators for monitoring activities and processes that are deemed high-risk, high-volume, or problem-prone. Appropriate evaluation of environmental monitoring might include, for example, the trending of an indicator such as settling plate counts. In general, the selection of indicators and the effectiveness of the overall QA plan should be reassessed on an annual basis.

[9] Other accepted terms that describe activities aimed at assessing and improving the quality of care rendered include Continuous Quality Improvement, Quality Assessment and Improvement, and Total Quality Management.

[10] The use of additional resources, such as the Accreditation Manual for Home Care from the Joint Commission on Accreditation of Healthcare Organizations, may prove helpful in the development of a QA plan.

SPECIFICATION FOR PULMICORT RESPULES

0.5 MG (0.25 MG/ML)

Document Number: RITA.000-243-420

Test procedure	Acceptance criteria	Method reference
Appearance	An easily resuspendable white to off-white suspension filled into single-dose units made of plastic.	RITA.000-156-246
Color of Solution:		RITA.000-156-247
Absorbance at 400 nm Absorbance at 450 nm	NMT 0.01 NMT 0.01	
pH	4.0 – 5.0	USP
Foreign Particulate Matter – Microscopy (average #/Unit)	Stage 1: NMT 10 foreign particles per ampoule >100 µm and no single particle >1,000 µm. Stage 2: If any particle >1,000 µm is observed when the test is applied to the original set of samples and the results from the first stage cannot be invalidated due to contamination introduced during analysis or sample preparation, repeat the test for Foreign Particulate Matter using double the number of representative samples. There shall be NMT 10 foreign particles per ampule >100 µm and no single particle >1,000 µm for all ampoules analyzed in stage two.	RITA.000-156-111
Foreign Particulate Matter – Light Obscuration	Number of foreign particulates in the 2–10 µm range: NMT 14,800 Number of foreign particulates in the 10–50 µm range: NMT 430 Number of foreign particulates in the 50–100 µm range: NMT 2	RITA.000-156-132
Osmolality	256–314 mOsm/kg	RITA.000-156-250

Test procedure	Acceptance criteria		Method reference
Identification for budesonide (IR)	Conforms to reference spectrum		RITA.000-156-292
Budesonide Assay	The average of 3 ampoules, each from a separate strip of ampoules is:		RITA.000-159-008
	Release	Shelf life	
	0.237-0.263 mg/mL	0.231-0.263 mg/mL	
Edetate disodium, dihydrate:	0.090–0.110 mg/mL		RITA.000-156-287
Content uniformity	Stage 1: Of 10 ampoules tested, AV ≤ L1 where: L1 (maximum allowed acceptance value) = 15.0 T (average of the limits for potency) = 100% If AV > L1, test an additional 20 (Stage 2) Stage 2: Of 30 ampoules tested, AV ≤ L1 where: L1 (maximum allowed acceptance value) = 15.0 T (average of the limits for potency) = 100% No dosage unit result can be LT 0.75M, while no result can be GT 1.25M, where M is the calculated reference value.		USP
Particle Measurement:			RITA.000-156-198
Mass Median Diameter	2.1-3.1 µm		
d <7.0 µm d <4.0 µm d <1.5 µm	NLT 95% (m/m) NLT 71% (m/m) NMT 25% (m/m		
Impurities and Degradation Products	Release	Shelf life	
Total	NMT 0.5% by area	NMT 0.8% by area	RITA.000-159-047
21-aldehyde of budesonide	NMT 0.2% by area	NMT 0.2% by area	RITA.000-159-047
17-carboxylic acid of budesonide	NMT 0.2% by area	NMT 0.2% by area	RITA.000-159-047
16-alpha hydroxy prednisolone	NMT 0.2% by area	NMT 0.2% by area	RITA.000-159-047

Test procedure	Acceptance criteria		Method reference
D-homobudesonide	NMT 0.1% by area	NMT 0.1% by area	RITA.000-159-047
14,15-dehydrobudesonide	NMT 0.1% by area	NMT 0.1% by area	RITA.000-159-047
Individual Unspecified Impurity	LT 0.10% by area	LT 0.10% by area	RITA.000-159-047
Total Unspecified Impurities	LT 0.10% by area	LT 0.10% by area	RITA.000-159-047
11-ketobudesonide	NMT 0.2% by area	NMT 0.2% by area	RITA.000-156-290
16,21-cyclic hemiacetal of 17-desoxyprednisolone	LT 0.10% by area	LT 0.10% by area	RITA.000-159-029
16,17-dehydro-21-hydroxyprednisolone	LT 0.10% by area	LT 0.10% by area	RITA.000-159-029
Leachables			
Ethanol		NMT 1 µg/g	RITA.000-176-912
Ethyl Acetate		NMT 2 µg/g	RITA.000-176-912
2,2,4,6,6 Pentamethylheptane		NMT 0.4 µg/g	RITA.000-176-912
Total Hydrocarbons C10 – C26		NMT 6 µg/mL	RITA.000-177-000
4-Toluene Sulfonamide [a]		NMT 0.4 µg/mL	RITA.000-176-966
4,4-Methylene Bis (Phenyl Isocyanate) [a]		NMT 1 µg/mL	RITA.000-176-966
Dioctyl Phthalate [a]		NMT 1 µg/mL	RITA.000-176-966
Irganox 1076 [a]		NMT 1 µg/mL	RITA.000-177-521
Acridine [a]		NMT 10 ng/mL	RITA.000-159-041
Sterility	Meets current USP <71>		USP

a For drug product packaged in Amcor Foil: if tested, will comply.

A weight class is chosen so that the tolerance of the weights used does not exceed 0.1% of the amount weighed. Generally, class 2 may be used for quantities greater than 20 mg, class 3 for quantities of greater than 50 mg, and class 4 for quantities of greater than 100 mg. Weights should be calibrated periodically, preferably against an absolute standard weight.

Microbiological Tests

⟨51⟩ ANTIMICROBIAL PRESERVATIVES—EFFECTIVENESS

Antimicrobial preservatives are substances added to dosage forms to protect them from microbial contamination. They are used primarily in multiple-dose containers to inhibit the growth of microorganisms that may be introduced inadvertently during or subsequent to the manufacturing process. Antimicrobial agents should not be used solely to reduce the viable microbial count as a substitute for good manufacturing practice. Situations may arise, however, where their use may be required to minimize proliferation of microorganisms. It should be recognized that the presence of dead microorganisms or the metabolic by-products of living microorganisms may cause adverse reactions in sensitized persons.

Any antimicrobial agent may exhibit the protective properties of a preservative. However, all useful antimicrobial agents are toxic substances. For maximum protection of the consumer, the concentration of the preservative shown to be effective in the final packaged product should be considerably below the concentrations of the preservative that may be toxic to human beings.

The following tests are provided to demonstrate, in multiple-dose parenteral, otic, nasal, and ophthalmic products made with aqueous bases or vehicles, the effectiveness of any added antimicrobial preservative(s), the presence of which is declared on the label of the product concerned. The tests and standards apply only to the product in the original, unopened container in which it was distributed by the producer.[1]

Test Organisms—Use cultures of the following microorganisms:[2] *Candida albicans* (ATCC No. 10231), *Aspergillus niger* (ATCC No. 16404), *Escherichia coli* (ATCC No. 8739), *Pseudomonas aeruginosa* (ATCC No. 9027), and *Staphylococcus aureus* (ATCC No. 6538). Other microorganisms, in addition to those listed, may be included in the test on an optional basis, especially if it appears likely that such microorganisms may represent contaminants likely to be introduced during use of the article.

Media—For the initial cultivation of the test organisms, select an agar medium that is favorable to vigorous growth of the respective stock culture, such as Soybean-Casein Digest Agar Medium (see under *Microbial Limit Tests* ⟨61⟩).

Preparation of Inoculum—Preparatory to the test, inoculate the surface of a suitable volume of solid agar medium from a recently grown stock culture of each of the specified microorganisms. Incubate the bacterial cultures at 30° to 35° for 18 to 24 hours, the culture of *C. albicans* at 20° to 25° for 48 hours, and the culture of *A. niger* at 20° to 25° for 1 week.

To harvest the bacterial and *C. albicans* cultures, use sterile saline TS, washing the surface growth into a suitable vessel, and add sufficient additional saline TS to reduce the microbial count to about 100 million microorganisms per mL. To harvest the *A. niger* culture, use sterile saline TS containing 0.05% of polysorbate 80, and adjust the spore count to about 100 million per mL by adding more sterile saline TS.

Alternatively, the stock culture organisms may be grown in a suitable liquid medium, and the cells may be harvested by centrifugation, washed, and resuspended in sterile saline TS to give the required microbial or spore count.

Determine the number of colony-forming units per mL in each suspension. This value serves to determine the size of inoculum to use in the test. If the standardized suspensions are not used promptly, periodically monitor the suspensions by the plate-count method to determine any loss of viability.

For the plate-count monitoring of inoculated test preparations, use an agar medium corresponding to that used for the initial cultivation of the respective microorganism. Where a specific inactivator of the preservative(s) is available, add a suitable amount of it to the agar plate count medium.

Procedure—Where the product container can be entered aseptically, such as with a needle and syringe through a rubber stopper, conduct the test in five original product containers. If the product container is such that it cannot be entered aseptically, transfer 20-mL samples of the product to each of five sterile, capped bacteriological tubes of suitable size. Inoculate each tube or product container with one of the standardized microbial suspensions, using a ratio equivalent to 0.10 mL of inoculum to 20 mL of product, and mix. A suitable concentration of test microorganisms should be added so that the concentration in the test preparation immediately after inoculation is between 100,000 and 1,000,000 microorganisms per mL. Determine the number of viable microorganisms in each inoculum suspension, and calculate the initial concentration of microorganisms per mL of product under test by the plate-count method.

Incubate the inoculated containers or tubes at 20° to 25°. Examine the containers or tubes at 7, 14, 21, and 28 days subsequent to inoculation. Record any changes observed in appearance, and determine by the plate-count procedure the number of viable microorganisms present at each of these time intervals. Using the theoretical concentrations of microorganisms present at the start of the test, calculate the percentage change in the concentration of each microorganism during the test.

Interpretation—The preservative is effective in the product examined if (a) the concentrations of viable bacteria are reduced to not more than 0.1% of the initial concentrations by the fourteenth day; (b) the concentrations of viable yeasts and molds remain at or below the initial concentrations during the first 14 days; and (c) the concentration of each test microorganism remains at or below these designated levels during the remainder of the 28-day test period.

⟨61⟩ MICROBIAL LIMIT TESTS

This chapter provides tests for the estimation of the number of viable aerobic microorganisms present and for freedom from designated microbial species in pharmaceutical articles of all kinds, from raw materials to the finished forms. An automated method may be substituted for the tests presented here, provided it has been properly validated as giving equivalent or better results. In preparing for and in applying the tests, observe aseptic precautions in handling the specimens. Unless otherwise directed, where the procedure specifies simply "incubate," hold the container in air that is thermostatically controlled at a temperature between 30° and 35°, for a period of 24 to 48 hours. The term "growth" is used in a special sense herein, i.e., to designate *the presence and presumed proliferation of viable microorganisms*.

Preparatory Testing

The validity of the results of the tests set forth in this chapter rests largely upon the adequacy of a demonstration that the test specimens to which they are applied do not, of themselves, inhibit the multiplication, under the test conditions, of microorganisms that may be present. Therefore, preparatory to conducting the tests on a regular basis and as circumstances require subsequently, inoculate diluted specimens of the material to be tested with separate viable cultures of *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Salmonella*. This can be done by adding 1 mL of not less than 10^{-3} dilution of a 24-hour broth culture of the microorganism to the first dilution (in

[1] For products made with nonaqueous (anhydrous) bases or vehicles, a suitable test may be feasible only at a particular stage in manufacture.

[2] Available from American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD 20852.

pH 7.2 Phosphate Buffer, Fluid Soybean–Casein Digest Medium, or Fluid Lactose Medium) of the test material and following the test procedure. Failure of the organism(s) to grow in the relevant medium invalidates that portion of the examination and necessitates a modification of the procedure by (1) an increase in the volume of diluent, the quantity of test material remaining the same, or by (2) the incorporation of a sufficient quantity of suitable inactivating agent(s) in the diluents, or by (3) an appropriate combination of modifications (1) and (2) so as to permit growth of the inocula.

The following are examples of ingredients and their concentrations that may be added to the culture medium to neutralize inhibitory substances present in the sample: soy lecithin, 0.5%; and polysorbate 20, 4.0%. Alternatively, repeat the test as described in the preceding paragraph, using Fluid Casein Digest–Soy Lecithin–Polysorbate 20 Medium to demonstrate neutralization of preservatives or other antimicrobial agents in the test material. Where inhibitory substances are contained in the product and the latter is soluble, a suitable, validated adaptation of a procedure set forth in the *Test Procedures Using Membrane Filtration*, under *Sterility Tests* ⟨71⟩, may be used.

If in spite of the incorporation of suitable inactivating agents and a substantial increase in the volume of diluent it is still not possible to recover the viable cultures described above and where the article is not suitable for employment of membrane filtration, it can be assumed that the failure to isolate the inoculated organism is attributable to the bactericidal activity of the product. This information serves to indicate that the article is not likely to be contaminated with the given species of microorganism. Monitoring should be continued in order to establish the spectrum of inhibition and bactericidal activity of the article.

Buffer Solution and Media

Culture media may be prepared as follows, or dehydrated culture media may be used provided that, when reconstituted as directed by the manufacturer or distributor, they have similar ingredients and/or yield media comparable to those obtained from the formulas given herein.

In preparing media by the formulas set forth herein, dissolve the soluble solids in the water, using heat, if necessary, to effect complete solution, and add solutions of hydrochloric acid or sodium hydroxide in quantities sufficient to yield the desired pH in the medium when it is ready for use. Determine the pH at 25 ± 2°.

Where agar is called for in a formula, use agar that has a moisture content of not more than 15%. Where water is called for in a formula, use *Purified Water*.

pH 7.2 Phosphate Buffer

Stock Solution—Dissolve 34 g of monobasic potassium phosphate in about 500 mL of water contained in a 1000-mL volumetric flask. Adjust to pH 7.2 ± 0.1 by the addition of sodium hydroxide TS (about 175 mL), add water to volume, and mix. Dispense and sterilize. Store under refrigeration.

For use, dilute the *Stock Solution* with water in the ratio of 1 to 800, and sterilize.

MEDIA

Unless otherwise indicated, the media should be sterilized by heating in an autoclave (see *Steam Sterilization* under *Sterilization* ⟨1211⟩), the exposure time depending on the volume to be sterilized.

I. Fluid Casein Digest–Soy Lecithin–Polysorbate 20 Medium

Pancreatic Digest of Casein	20 g
Soy Lecithin	5 g
Polysorbate 20	40 mL
Water	960 mL

Dissolve the pancreatic digest of casein and soy lecithin in 960 mL of water, heating in a water bath at 48° to 50° for about 30 minutes to effect solution. Add 40 mL of polysorbate 20. Mix, and dispense as desired.

II. Soybean-Casein Digest Agar Medium

Pancreatic Digest of Casein	15.0 g
Papaic Digest of Soybean Meal	5.0 g
Sodium Chloride	5.0 g
Agar	15.0 g
Water	1000 mL

pH after sterilization: 7.3 ± 0.2.

III. Fluid Soybean-Casein Digest Medium

Prepare as directed for *Soybean-Casein Digest Medium* under *Sterility Tests* ⟨71⟩.

IV. Mannitol-Salt Agar Medium

Pancreatic Digest of Casein	5.0 g
Peptic Digest of Animal Tissue	5.0 g
Beef Extract	1.0 g
D-Mannitol	10.0 g
Sodium Chloride	75.0 g
Agar	15.0 g
Phenol Red	0.025 g
Water	1000 mL

Mix, then heat with frequent agitation, and boil for 1 minute to effect solution.

pH after sterilization: 7.4 ± 0.2.

V. Baird-Parker Agar Medium

Pancreatic Digest of Casein	10.0 g
Beef Extract	5.0 g
Yeast Extract	1.0 g
Lithium Chloride	5.0 g
Agar	20.0 g
Glycine	12.0 g
Sodium Pyruvate	10.0 g
Water	950 mL

Heat with frequent agitation, and boil for 1 minute. Sterilize, cool to between 45° and 50°, and add 10 mL of sterile potassium tellurite solution (1 in 100) and 50 mL of egg-yolk emulsion. Mix intimately but gently, and pour into plates. (Prepare the egg-yolk emulsion by disinfecting the surface of whole shell eggs, aseptically cracking the eggs, and separating out intact yolks into a sterile graduated cylinder. Add sterile saline TS to obtain a 3 to 7 ratio of egg yolk to saline. Add to a sterile blender cup, and mix at high speed for 5 seconds.)

pH after sterilization: 6.8 ± 0.2.

VI. Vogel-Johnson Agar Medium

Pancreatic Digest of Casein	10.0 g
Yeast Extract	5.0 g
Mannitol	10.0 g
Dibasic Potassium Phosphate	5.0 g
Lithium Chloride	5.0 g
Glycine	10.0 g
Agar	16.0 g
Phenol Red	25.0 mg
Water	1000 mL

Boil the solution of solids for 1 minute. Sterilize, cool to between 45° and 50°, and add 20 mL of sterile potassium tellurite solution (1 in 100).

pH after sterilization: 7.2 ± 0.2.

VII. Cetrimide Agar Medium

Pancreatic Digest of Gelatin	20.0 g
Magnesium Chloride	1.4 g
Potassium Sulfate	10.0 g
Agar	13.6 g
Cetyl Trimethylammonium Bromide (Cetrimide)	0.3 g
Glycerin	10.0 mL
Water	1000 mL

Dissolve all solid components in the water, and add the glycerin. Heat, with frequent agitation, and boil for 1 minute to effect solution.

pH after sterilization: 7.2 ± 0.2.

VIII. Pseudomonas Agar Medium for Detection of Fluorescin

Pancreatic Digest of Casein	10.0 g
Peptic Digest of Animal Tissue	10.0 g

Anhydrous Dibasic Potassium Phosphate	1.5 g
Magnesium Sulfate ($MgSO_4 \cdot 7H_2O$)	1.5 g
Glycerin	10.0 mL
Agar	15.0 g
Water	1000 mL

Dissolve the solid components in the water before adding the glycerin. Heat, with frequent agitation, and boil for 1 minute to effect solution.

pH after sterilization: 7.2 ± 0.2.

IX. Pseudomonas Agar Medium for Detection of Pyocyanin

Pancreatic Digest of Gelatin	20.0 g
Anhydrous Magnesium Chloride	1.4 g
Anhydrous Potassium Sulfate	10.0 g
Agar	15.0 g
Glycerin	10.0 mL
Water	1000 mL

Dissolve the solid components in the water before adding the glycerin. Heat, with frequent agitation, and boil for 1 minute to effect solution.

pH after sterilization: 7.2 ± 0.2.

X. Fluid Lactose Medium

Beef Extract	3.0 g
Pancreatic Digest of Gelatin	5.0 g
Lactose	5.0 g
Water	1000 mL

Cool as quickly as possible after sterilization.

pH after sterilization: 6.9 ± 0.2.

XI. Fluid Selenite-Cystine Medium

Pancreatic Digest of Casein	5.0 g
Lactose	4.0 g
Sodium Phosphate	10.0 g
Sodium Acid Selenite	4.0 g
L-Cystine	10.0 mg
Water	1000 mL

Final pH: 7.0 ± 0.2.

Mix, and heat to effect solution. Heat in flowing steam for 15 minutes. *Do not sterilize.*

XII. Fluid Tetrathionate Medium

Pancreatic Digest of Casein	2.5 g
Peptic Digest of Animal Tissue	2.5 g
Bile Salts	1.0 g
Calcium Carbonate	10.0 g
Sodium Thiosulfate	30.0 g
Water	1000 mL

Heat the solution of solids to boiling. On the day of use, add a solution prepared by dissolving 5 g of potassium iodide and 6 g of iodine in 20 mL of water. Then add 10 mL of a solution of brilliant green (1 in 1000), and mix. Do not heat the medium after adding the brilliant green solution.

XIII. Brilliant Green Agar Medium

Yeast Extract	3.0 g
Peptic Digest of Animal Tissue	5.0 g
Pancreatic Digest of Casein	5.0 g
Lactose	10.0 g
Sodium Chloride	5.0 g
Sucrose	10.0 g
Phenol Red	80 mg
Agar	20.0 g
Brilliant Green	12.5 mg
Water	1000 mL

Boil the solution of solids for 1 minute. Sterilize just prior to use, melt the medium, pour into Petri dishes, and allow to cool.

pH after sterilization: 6.9 ± 0.2.

XIV. Xylose-Lysine-Desoxycholate Agar Medium

Xylose	3.5 g
L-Lysine	5.0 g
Lactose	7.5 g
Sucrose	7.5 g
Sodium Chloride	5.0 g
Yeast Extract	3.0 g
Phenol Red	80 mg
Agar	13.5 g
Sodium Desoxycholate	2.5 g
Sodium Thiosulfate	6.8 g
Ferric Ammonium Citrate	800 mg
Water	1000 mL

Final pH: 7.4 ± 0.2.

Heat the mixture of solids and water, with swirling, just to the boiling point. *Do not overheat or sterilize.* Transfer at once to a water bath maintained at about 50°, and pour into plates as soon as the medium has cooled.

XV. Bismuth Sulfite Agar Medium

Beef Extract	5.0 g
Pancreatic Digest of Casein	5.0 g
Peptic Digest of Animal Tissue	5.0 g
Dextrose	5.0 g
Sodium Phosphate	4.0 g
Ferrous Sulfate	300 mg
Bismuth Sulfite Indicator	8.0 g
Agar	20.0 g
Brilliant Green	25 mg
Water	1000 mL

Final pH: 7.6 ± 0.2.

Heat the mixture of solids and water, with swirling, just to the boiling point. *Do not overheat or sterilize.* Transfer at once to a water bath maintained at about 50°, and pour into plates as soon as the medium has cooled.

XVI. Triple Sugar-Iron-Agar Medium

Pancreatic Digest of Casein	10.0 g
Pancreatic Digest of Animal Tissue	10.0 g
Lactose	10.0 g
Sucrose	10.0 g
Dextrose	1.0 g
Ferrous Ammonium Sulfate	200 mg
Sodium Chloride	5.0 g
Sodium Thiosulfate	200 mg
Agar	13.0 g
Phenol Red	25 mg
Water	1000 mL

pH after sterilization: 7.3 ± 0.2.

XVII. MacConkey Agar Medium

Pancreatic Digest of Gelatin	17.0 g
Pancreatic Digest of Casein	1.5 g
Peptic Digest of Animal Tissue	1.5 g
Lactose	10.0 g
Bile Salts Mixture	1.5 g
Sodium Chloride	5.0 g
Agar	13.5 g
Neutral Red	30 mg
Crystal Violet	1.0 mg
Water	1000 mL

Boil the mixture of solids and water for 1 minute to effect solution.

pH after sterilization: 7.1 ± 0.2.

XVIII. Levine Eosin–Methylene Blue Agar Medium

Pancreatic Digest of Gelatin	10.0 g
Dibasic Potassium Phosphate	2.0 g
Agar	15.0 g
Lactose	10.0 g
Eosin Y	400 mg
Methylene Blue	65 mg
Water	1000 mL

Dissolve the pancreatic digest of gelatin, the dibasic potassium phosphate, and the agar in the water, with warming, and allow to cool. Just prior to use, liquefy the gelled agar solution, add the remaining ingredients, as solutions, in the following amounts, and mix: for each 100 mL of the liquefied agar solution—5 mL of lactose solution (1 in 5), 2 mL of the eosin Y solution (1 in 50), and 2 mL of methylene blue solution (1 in 300). The finished medium may not be clear.

pH after sterilization: 7.1 ± 0.2.

XIX. Sabouraud Dextrose Agar Medium

Dextrose	40 g
Mixture of equal parts of Peptic Digest of Animal Tissue and Pancreatic Digest of Casein	10 g
Agar	15 g
Water	1000 mL

Mix, and boil to effect solution.
pH after sterilization: 5.6 ± 0.2.

XX. Potato Dextrose Agar Medium

Cook 300 g of peeled and diced potatoes in 500 mL of water prepared by distillation, filter through cheesecloth, add water prepared by distillation to make 1000 mL, and add the following:

Agar	15 g
Glucose	20 g

Dissolve by heating, and sterilize.
pH after sterilization: 5.6 ± 0.2.
For use, just prior to pouring the plates, adjust the melted and cooled to 45° medium with sterile tartaric acid solution (1 in 10) to a pH of 3.5 ± 0.1. Do not reheat the pH 3.5 medium.

Sampling

Provide separate 10-mL or 10-g specimens for each of the tests called for in the individual monograph.

Procedure

Prepare the specimen to be tested, by treatment that is appropriate to its physical characteristics and that does not alter the number and kind of microorganisms originally present, in order to obtain a solution or suspension of all or part of it in a form suitable for the test procedure(s) to be carried out.

For a solid that dissolves to an appreciable extent but not completely, reduce the substance to a moderately fine powder, suspend it in the vehicle specified, and proceed as directed under *Total Aerobic Microbial Count*, and under *Test for Staphylococcus aureus and Pseudomonas aeruginosa* and *Test for Salmonella Species and Escherichia coli*.

For a fluid specimen that consists of a true solution, or a suspension in water or a hydroalcoholic vehicle containing less than 30 percent of alcohol, and for a solid that dissolves readily and practically completely in 90 mL of *pH 7.2 Phosphate Buffer* or the media specified, proceed as directed under *Total Aerobic Microbial Count*, and under *Test for Staphylococcus aureus and Pseudomonas aeruginosa* and *Test for Salmonella Species and Escherichia coli*.

For water-immiscible fluids, ointments, creams, and waxes, prepare a suspension with the aid of a minimal quantity of a suitable, sterile emulsifying agent (such as one of the polysorbates), using a mechanical blender and warming to a temperature not exceeding 45°, if necessary, and proceed with the suspension as directed under *Total Aerobic Microbial Count*, and under *Test for Staphylococcus aureus and Pseudomonas aeruginosa* and *Test for Salmonella Species and Escherichia coli*.

For a fluid specimen in aerosol form, chill the container in an alcohol–dry ice mixture for approximately 1 hour, cut open the container, allow it to reach room temperature, permit the propellant to escape, or warm to drive off the propellant if feasible, and transfer the quantity of test material required for the procedures specified in one of the two preceding paragraphs, as appropriate. Where 10.0 g or 10.0 mL of the specimen, whichever is applicable, cannot be obtained from 10 containers in aerosol form, transfer the entire contents from 10 chilled containers to the culture medium, permit the propellant to escape, and proceed with the test on the residues. If the results of the test are inconclusive or doubtful, repeat the test with a specimen from 20 more containers.

Total Aerobic Microbial Count—For specimens that are sufficiently soluble or translucent to permit use of the *Plate Method*, use that method; otherwise, use the *Multiple-tube Method*. With either method, first dissolve or suspend 10.0 g of the specimen if it is a solid, or 10 mL, accurately measured, if the specimen is a liquid, in pH 7.2 Phosphate Buffer, Fluid Soybean-Casein Digest Medium, or Fluid Casein Digest–Soy Lecithin–Polysorbate 20 Medium to make 100 mL. For viscous specimens that cannot be pipeted at this initial 1 : 10 dilution, dilute the specimen until a suspension is obtained, i.e., 1 : 50 or 1 : 100, etc., that can be pipeted. Perform the test for absence of inhibitory (antimicrobial) properties as described under *Preparatory Testing* before the determination of *Total Aerobic Microbial Count*. Add the specimen to the medium not more than 1 hour after preparing the appropriate dilutions for inoculation.

PLATE METHOD—Dilute further, if necessary, the fluid so that 1 mL will be expected to yield between 30 and 300 colonies. Pipet 1 mL of the final dilution onto each of two sterile petri dishes. Promptly add to each dish 15 to 20 mL of Soybean-Casein Digest Agar Medium that previously has been melted and cooled to approximately 45°. Cover the petri dishes, mix the sample with the agar by tilting or rotating the dishes, and allow the contents to solidify at room temperature. Invert the petri dishes, and incubate for 48 to 72 hours. Following incubation, examine the plates for growth, count the number of colonies, and express the average for the two plates in terms of the number of microorganisms per g or per mL of specimen. If no microbial colonies are recovered from the dishes representing the initial 1 : 10 dilution of the specimen, express the results as "less than 10 microorganisms per g or per mL of specimen."

MULTIPLE-TUBE METHOD—Into each of fourteen test tubes of similar size place 9.0 mL of sterile Fluid Soybean-Casein Digest Medium. Arrange twelve of the tubes in four sets of three tubes each. Put aside one set of three tubes to serve as the controls. Into each of three tubes of one set ("100") and into a fourth tube (*A*) pipet 1 mL of the solution or suspension of the specimen, and mix. From tube *A*, pipet 1 mL of its contents into the one remaining tube (*B*) not included in a set, and mix. These two tubes contain 100 mg (or 100 µL) and 10 mg (or 10 µL) of the specimen, respectively. Into each of the second set ("10") of three tubes pipet 1 mL from tube *A*, and into each tube of the third set ("1") pipet 1 mL from tube *B*. Discard the unused contents of tubes *A* and *B*. Close well, and incubate all of the tubes. Following the incubation period, examine the tubes for growth: the three control tubes remain clear and the observations in the tubes containing the specimen, when interpreted by reference to Table 1, indicate the most probable number of microorganisms per g or per mL of specimen.

Table 1. Most Probable Total Count by Multiple-tube Method.

Observed Combinations of Numbers of Tubes Showing Growth in Each Set			
No. of mg (or mL) of Specimen per Tube			Most Probable Number of Microorganisms per g or per mL
100 (100 µL)	10 (10 µL)	1 (1 µL)	
3	3	3	>1100
3	3	2	1100
3	3	1	500
3	3	0	200
3	2	3	290
3	2	2	210
3	2	1	150
3	2	0	90
3	1	3	160
3	1	2	120
3	1	1	70
3	1	0	40
3	0	3	95
3	0	2	60
3	0	1	40
3	0	0	23

Test for *Staphylococcus aureus* and *Pseudomonas aeruginosa*—To the specimen add Fluid Soybean-Casein Digest Medium to make 100 mL, mix, and incubate. Examine the medium for growth, and if growth is present, use an inoculating loop to streak a portion of the medium on the surface of Vogel-Johnson Agar Medium (or Baird-Parker Agar Medium, or Mannitol-Salt Agar Medium) and of Cetrimide Agar Medium, each plated on petri dishes. Cover and invert the dishes, and incubate. If, upon examination, none of the plates contains colonies having the char-

acteristics listed in Tables 2 and 3 for the media used, the test specimen meets the requirements for freedom from *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

COAGULASE TEST (FOR *Staphylococcus aureus*)—With the aid of an inoculating loop, transfer representative suspect colonies from the agar surfaces of the Vogel-Johnson Agar Medium (or Baird-Parker Agar Medium, or Mannitol-Salt Agar Medium) to individual tubes, each containing 0.5 mL of mammalian, preferably rabbit or horse, plasma with or without suitable additives. Incubate in a water bath at 37°, examining the tubes at 3 hours and subsequently at suitable intervals up to 24 hours. Test positive and negative controls simultaneously with the unknown specimens. If no coagulation in any degree is observed, the specimen meets the requirements of the test for absence of *Staphylococcus aureus*.

OXIDASE AND PIGMENT TESTS (FOR *Pseudomonas aeruginosa*)—With the aid of an inoculating loop, streak representative suspect colonies from the agar surface of Cetrimide Agar Medium on the agar surfaces of Pseudomonas Agar Medium for Detection of Fluorescin and Pseudomonas Agar Medium for Detection of Pyocyanin contained in petri dishes. If numerous colonies are to be transferred, divide the surface of each plate into quadrants, each of which may be inoculated from a separate colony. Cover and invert the inoculated media, and incubate at 35 ± 2° for not less than three days. Examine the streaked surfaces under ultraviolet light. Examine the plates to determine whether colonies having the characteristics listed in Table 3 are present.

Confirm any suspect colonial growth on one or more of the media as *Pseudomonas aeruginosa* by means of the oxidase test. Upon the colonial growth place or transfer colonies to strips or disks of filter paper that previously has been impregnated with *N,N*-dimethyl-*p*-phenylenediamine dihydrochloride: if there is no development of a pink color, changing to purple, the specimen meets the requirements of the test for the absence of *Pseudomonas aeruginosa*. The presence of *Pseudomonas aeruginosa* may be confirmed by other suitable cultural and biochemical tests, if necessary.

Table 2. Morphologic Characteristics of *Staphylococcus aureus* on Selective Agar Media.

Selective Medium	Characteristic Colonial Morphology	Gram Stain
Vogel-Johnson Agar Medium	Black Surrounded by yellow zone	Positive cocci (in clusters)
Mannital-Salt Agar Medium	Yellow colonies with yellow zones	Positive cocci (in clusters)
Baird-Parker Agar Medium	Black, shiny, surrounded by clear zones 2 to 5 mm	Positive cocci (in clusters)

Table 3. Morphologic Characteristics of *Pseudomonas aeruginosa* on Selective and Diagnostic Agar Media.

Selective Medium	Characteristic Colonial Morphology	Fluorescence in Ultraviolet Light	Oxidase Test	Gram Stain
Centrimide Agar Medium	Generally greenish	Greenish	Positive	Negative rods
Pseudomonas Agar Medium for Detection of Fluorescin	Generally colorless to yellowish	Yellowish	Positive	Negative rods
Pseudomonas Agar Medium for Detection of Pyocyanin	Generally greenish	Blue	Positive	Negative rods

Test for *Salmonella* Species and *Escherichia coli*—To the specimen, contained in a suitable vessel, add a volume of Fluid Lactose Medium to make 100 mL, and incubate. Examine the medium for growth, and if growth is present, mix by gently shaking. Pipet 1-mL portions into vessels containing, respectively, 10 mL of Fluid Selenité-Cystine Medium and Fluid Tetrathionate Medium, mix, and incubate for 12 to 24 hours. (Retain the remainder of the Fluid Lactose Medium.)

TEST FOR *Salmonella* SPECIES—By means of an inoculating loop, streak portions from both the selenite-cystine and tetrathionate media on the surface of Brilliant Green Agar Medium, Xylose-Lysine-Desoxycholate Agar Medium, and Bismuth Sulfite Agar Medium contained in petri dishes. Cover and invert the dishes, and incubate. Upon examination, if none of the colonies conforms to the description given in Table 4, the specimen meets the requirements of the test for absence of the genus *Salmonella*.

If colonies of Gram-negative rods matching the description in Table 4 are found, proceed with further identification by transferring representative suspect colonies individually, by means of an inoculating wire, to a butt-slant tube of Triple Sugar-Iron-Agar Medium by first streaking the surface of the slant and then stabbing the wire well beneath the surface. Incubate. If examination discloses no evidence of tubes having alkaline (red) slants and acid (yellow) butts (with or without concomitant blackening of the butt from hydrogen sulfide production), the specimen meets the requirements of the test for the absence of the genus *Salmonella*.*

* Additional, confirmatory evidence may be obtained by use of procedures set forth in *Official Methods of Analysis of the AOAC*, 12th ed. (1975), sections 46.013–46.026.

TEST FOR *Escherichia coli*—By means of an inoculating loop, streak a portion from the remaining Fluid Lactose Medium on the surface of MacConkey Agar Medium. Cover and invert the dishes, and incubate. Upon examination, if none of the colonies conforms to the description given in Table 5 for this medium, the specimen meets the requirements of the test for absence of *Escherichia coli*.

Table 4. Morphologic Characteristics of *Salmonella* Species on Selective Agar Media.

Selective Medium	Characteristic Colonial Morphology
Brilliant Green Agar Medium	Small, transparent, colorless or pink to white opaque (frequently surrounded by pink to red zone)
Xylose-Lysine-Desoxycholate Agar Medium	Red, with or without black centers
Bismuth Sulfite Agar Medium	Black or green

Table 5. Morphologic Characteristics of *Escherichia coli* on MacConkey Agar Medium.

Gram Stain	Characteristic Colonial Morphology
Negative rods (cocco-bacilli)	Brick-red; may have surrounding zone of precipitated bile

If colonies matching the description in Table 5 are found, proceed with further identification by transferring the suspect colonies individually, by means of an inoculating loop, to the surface of Levine Eosin–Methylene Blue Agar Medium, plated on petri dishes. If numerous colonies are to be transferred, divide the surface of each plate into quadrants, each of which may be seeded from a separate colony. Cover and invert the plates, and incubate. Upon examination, if none of the colonies exhibits both a characteristic metallic sheen under reflected light and a blue-black appearance under transmitted light, the specimen meets the requirements of the test for the absence of *Escherichia coli*. The presence of *Escherichia coli* may be confirmed by further suitable cultural and biochemical tests.

Total Combined Molds and Yeasts Count—Proceed as for the *Plate Method* under *Total Aerobic Microbial Count*, except for using the same amount of Sabouraud Dextrose Agar Medium or Potato Dextrose Agar Medium, instead of Soybean Casein Digest Medium, and except for incubating the inverted petri dishes for 5 to 7 days at 20° to 25°.

Retest—For the purpose of confirming a doubtful result by any of the procedures outlined in the foregoing tests following their application to a 10.0-g specimen, a retest on a 25-g specimen of the product may be conducted. Proceed as directed under *Procedure*, but make allowance for the larger specimen size.

⟨71⟩ STERILITY TESTS

The following procedures are applicable for determining whether a Pharmacopeial article purporting to be sterile complies with the requirements set forth in the individual monograph with respect to the test for *Sterility*. (For the use of sterility test procedures as part of quality control in manufacture, see *Sterilization and Sterility Assurance of Compendial Articles* ⟨1211⟩.) In view of the possibility that positive results may be due to faulty aseptic techniques or environmental contamination in testing, provisions are included under *Interpretation of Sterility Test Results* for two stages of testing.

Alternative procedures may be employed to demonstrate that an article is sterile, provided the results obtained are at least of equivalent reliability. (See *Procedures* under *Tests and Assays* in the *General Notices and Requirements*.) Where a difference appears, or in the event of a dispute, when evidence of microbial contamination is obtained by the procedure given in this Pharmacopeia, the result so obtained is conclusive of failure of the article to meet the requirements of the test. Similarly, failure to demonstrate microbial contamination by the procedure given in this Pharmacopeia is evidence that the article meets the requirements of the test. For additional interpretive information, see *Sterilization and Sterility Assurance of Compendial Articles* ⟨1211⟩.

Media

Media for the tests may be prepared as described below, or dehydrated mixtures yielding similar formulations may be used provided that, when reconstituted as directed by the manufacturer or distributor, they have growth-promoting properties equal or superior to those obtained from the formulas given herein.

I. Fluid Thioglycollate Medium

L-Cystine	0.5 g
Sodium Chloride	2.5 g
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	5.5 g
Agar, granulated (moisture content not in excess of 15%)	0.75 g
Yeast Extract (water-soluble)	5.0 g
Pancreatic Digest of Casein	15.0 g
Sodium Thioglycollate	0.5 g
or Thioglycollic Acid	0.3 mL
Resazurin Sodium Solution (1 in 1000), freshly prepared	1.0 mL
Water	1000 mL

pH after sterilization: 7.1 ± 0.2.

Mix, and heat until solution is effected. Adjust the solution with 1 *N* sodium hydroxide so that, after sterilization, it will have a pH of 7.1 ± 0.2. Filter while hot through filter paper, if necessary. Place the medium in suitable vessels that provide a ratio of surface to depth of medium such that not more than the upper half of the medium has undergone a color change indicative of oxygen uptake at the end of the incubation period. Sterilize in an autoclave. If more than the upper one-third has acquired a pink color, the medium may be restored once by heating on a steam bath or in free-flowing steam until the pink color disappears. When ready for use, not more than the upper one-tenth of the medium should have a pink color.

Use Fluid Thioglycollate Medium by incubating it under aerobic conditions.

II. Alternative Thioglycollate Medium for Devices Having Tubes with Small Lumina

L-Cystine	0.5 g
Sodium Chloride	2.5 g
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	5.5 g
Yeast Extract (water-soluble)	5.0 g
Pancreatic Digest of Casein	15.0 g
Sodium Thioglycollate	0.5 g
or Thioglycollic Acid	0.3 mL
Water	1000 mL

pH after sterilization: 7.1 ± 0.2.

Heat the ingredients in a suitable container until solution is effected. Mix, and, if necessary, adjust the solution with 1 *N* sodium hydroxide so that, after sterilization, it will have a pH of 7.1 ± 0.2. Filter, if necessary, place in suitable vessels, and sterilize by steam. The medium is freshly prepared or heated in a steam bath and allowed to cool just prior to use. Do not reheat.

Use Alternative Thioglycollate Medium in a manner that will assure anaerobic conditions for the duration of the incubation period.

III. Soybean-Casein Digest Medium

Pancreatic Digest of Casein	17.0 g
Papaic Digest of Soybean Meal	3.0 g
Sodium Chloride	5.0 g
Dibasic Potassium Phosphate	2.5 g
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	2.5 g
Water	1000 mL

pH after sterilization: 7.3 ± 0.2.

Dissolve the solids in the water, warming slightly to effect solution. Cool the solution to room temperature, and adjust with 1 *N* sodium hydroxide, if necessary, to obtain a pH of 7.3 ± 0.2 after sterilization. Filter, if necessary, and dispense into suitable vessels. Sterilize by steam.

Use Soybean-Casein Digest Medium by incubating it under aerobic conditions.

NOTE—Where Fluid Thioglycollate Medium and Soybean-Casein Digest Medium are to be used in *Test Procedures for Direct Transfer to Test Media* applied to a specimen of the penicillin or cephalosporin class of antibiotic, aseptically transfer to each tube of Medium a quantity of penicillinase sufficient to inactivate the amount of antibiotic in the specimen under test. Determine the appropriate quantity of penicillinase to use for this purpose by using a penicillinase preparation that has been assayed previously for its penicillin- or cephalosporin-inactivating power. Or confirm that the appropriate quantity of penicillinase has been transferred to a tube of Fluid Thioglycollate Medium by adding to it an amount of penicillin or cephalosporin antibiotic equivalent to the amount of antibiotic in the specimen under test, inoculating the Medium with 1 mL of a 1:1000 dilution of an 18- to 24-hour culture of *Staphylococcus aureus* (ATCC 29737) in Fluid Thioglycollate Medium, and incubating it for 24 hours at 30° to 35°; at this time typical microbial growth must be observed. Perform this confirmatory test in an area completely separate from that used for sterility testing.

Diluting and Rinsing Fluids

FLUID A—Dissolve 1 g of peptic digest of animal tissue (see *Reagent Specifications* in the section *Reagents, Indicators, and Solutions*) in water to make 1 liter, filter or centrifuge to clarify, adjust to a pH of 7.1 ± 0.2, dispense into containers in 100-mL quantities, and sterilize by steam. [NOTE—Where *Fluid A* is to be used in performing the test for *Sterility* on a specimen of the

ASTRA
ASTRA DRACO

SPECIFICATION

Date 17 Sept 1997 Product Company Astra Draco Approved by Prepared by	PULMICORT 200 TURBUHALER powder inhaler, 200 doses	Specification No 21-515-53/9 Supersedes Specification No 21-515-53/8

	Description	White to off-white rounded granules, which disintegrate to a fine powder upon slight pressure, filled into a specially designed inhaler made of plastic materials. On the bottom of the turning grip, **Pulmicort™ 200 mcg** is embossed. The colour of the turning grip is brown. The colour of the cover is white. The nominal amount of budesonide delivered from the inhaler is 160 µg (label claim).
	Note	Items 1 and 2 shall be approved for each subbatch before items 3 - 12 are performed. Items 1 and 2 are performed only at the release occasion.
		Requirements
1	Delivered dose, dose 1	Release: For each of 30 inhalers, primed by two actuations, the amount of budesonide delivered from the mouthpiece in the first dose after priming is measured at an airflow of 60 l/min for 2 seconds. The requirements are met if - not more than 2 of the 30 values are outside 104 - 216 µg (± 35 % of label claim) and - no value is outside 80 - 240 µg (± 50 % of label claim). The average of the 30 doses should be 150 - 183 µg budesonide/dose (94 - 114 % of label claim).
2	Fine particle dose (MLI)	Release: Average of 3 measurements, each a composite (30 doses) of the 10 first doses from 3 inhalers primed by two actuations. 89 - 112 µg budesonide/dose (56 - 70 % of label claim) penetrates stage 2 and is deposited in stages 3-5 of the Multi-stage Liquid Impinger at an airflow of 60 l/min. The result from each measurement should be reported.

Date 17 Sept 1997 Product Company Astra Draco Approved by Prepared by	PULMICORT 200 TURBUHALER powder inhaler, 200 doses	Specification No 21-515-53/9 Supersedes Specification No 21-515-53/8

3	Appearance	A specially designed powder inhaler made of plastic materials. On the bottom of the turning grip, **Pulmicort™ 200 mcg** is embossed. The colour of the turning grip is brown. The colour of the cover is white. The contents are white to off-white rounded granules, which disintegrate to a fine powder upon slight pressure. A powder fraction may be present.
4	Colour of solution	The absorbance of a 1.5 per cent solution of the contents in methanol, determined in a 5 cm cell, is not more than 0.15 at 400 nm 0.04 at 450 nm
5	Budesonide (identity)	Positive identity.
6	Weight of contents	For each of 10 inhalers the amount of substance is quantitatively determined. The requirements are met if no value is outside 87 - 126 mg. If one value is outside 87 - 126 mg and no value is outside 82 - 131 mg, then 20 additional inhalers are tested. The requirements are met if not more than one of the 30 values is outside 87 - 126 mg and no value is outside 82 - 131 mg.
7	Delivered dose (uniformity)	Release: For each of 30 inhalers, primed by two actuations, the amount of budesonide delivered from the mouthpiece in the first dose after priming and the 200:th dose after priming are measured at an airflow of 60 l/min for 2 seconds. The requirements are met if - not more than 5 of the 60 values are outside 104 - 216 µg (± 35 % of label claim) and - no value is outside 80 - 240 µg (± 50 % of label claim).

Date 17 Sept 1997 Product Company Astra Draco Approved by Prepared by	PULMICORT 200 TURBUHALER powder inhaler, 200 doses	Specification No 21-515-53/9 Supersedes Specification No 21-515-53/8

7	Delivered dose (uniformity) (cont.)	Shelf life: For each of 10 inhalers, primed by two actuations, the amount of budesonide delivered from the mouthpiece in the first dose after priming and the 200:th dose after priming are measured at an airflow of 60 l/min for 2 seconds. The requirements are met if - not more than 2 of the 20 values are outside 104 - 216 µg (± 35 % of label claim) and no value is outside 80 - 240 µg (± 50 % of label claim). If - 3 to 6 values are outside 104 - 216 µg (± 35 % of label claim) or if the average of the 20 values is outside 136 - 184 µg budesonide/dose (± 15 % of label claim) - and no value is outside 80 - 240 µg (± 50 % of label claim) then 20 additional inhalers are tested. The requirements are met if - not more than 6 of the 60 values are outside 104 - 216 µg (± 35 % of label claim) and no value is outside 80 - 240 µg (± 50 % of label claim).
8	Delivered dose (average)	Average from uniformity testing. Release: (30 inhalers) 144 - 176 µg budesonide/dose (± 10 % of label claim). Shelf life: (10 or 30 inhalers) 136 - 184 µg budesonide/dose (± 15 % of label claim).
9	Aerodynamic particle size	Release: For each of 3 inhalers, primed by two actuations, composites of doses 1-10 and 191-200 are separately tested using the Andersen sampler at an airflow of 60 l/min. The following requirements apply to each composite of 10 doses (average of three inhalers). a. *Fine particle dose:* 81 - 111 µg budesonide/dose (51-69 % of label claim) penetrates stage 0 and is deposited in stages 1, 2, 3, 4, 5 and filter.

Date 17 Sept 1997 Product Company Astra Draco Approved by Prepared by	PULMICORT 200 TURBUHALER powder inhaler, 200 doses	Specification No 21-515-53/9 Supersedes Specification No 21-515-53/8

9	Aerodynamic particle size (cont.)	b. *Midstack particle dose:* 56 - 84 µg budesonide/dose (35-52 % of label claim) penetrates stage 1 and is deposited in stages 2, 3 and 4. c. *Submicron particle dose:* Not more than 6 µg budesonide/dose (≤ 3.8 % of label claim) penetrates stage 5 and is deposited in the filter. d. *Mass median aerodynamic diameter:* 2.2-2.7 µm for budesonide particles that penetrate the preseparator. e. *Geometric standard deviation:* 1.6-1.8 for budesonide particles that penetrate the preseparator. The following requirement applies to all fine particle doses measured (average of three inhalers). f. *Fine particle dose, average:* 84 - 106 µg budesonide/dose (53-66 % of label claim). If any of the requirements a-f is not fulfilled, 6 further inhalers are tested for this particular requirement. The average of 9 inhalers must fulfil the requirement. Shelf life: For each of 3 inhalers, primed by two actuations, composites of doses 1-10 and 191-200 are separately tested using the Andersen sampler at an airflow of 60 l/min. The following requirements apply to each composite of 10 doses (average of three inhalers). a. *Fine particle dose:* 81 - 130 µg budesonide/dose (51-81 % of label claim) penetrates stage 0 and is deposited in stages 1, 2, 3, 4, 5 and filter. b. *Midstack particle dose:* 56 - 101 µg budesonide/dose (35-63 % of label claim) penetrates stage 1 and is deposited in stages 2, 3 and 4. c. *Submicron particle dose:* Not more than 7 µg budesonide/dose (≤ 4 % of label claim) penetrates stage 5 and is deposited in the filter.

Date 17 Sept 1997 Product Company Astra Draco Approved by Prepared by	PULMICORT 200 TURBUHALER powder inhaler, 200 doses	Specification No 21-515-53/9 Supersedes Specification No 21-515-53/8

9	Aerodynamic particle size (cont.)	*d. Mass median aerodynamic diameter:* 2.1-2.7 µm for budesonide particles that penetrate the preseparator. *e. Geometric standard deviation:* 1.5-1.8 for budesonide particles that penetrate the preseparator. The following requirement applies to all fine particle doses measured (average of three inhalers). *f. Fine particle dose, average:* 84 - 120 µg budesonide/dose (53-75 % of label claim). If any of the requirements a-f is not fulfilled, 6 further inhalers are tested for this particular requirement. The average of 9 inhalers must fulfil the requirement.
10	Related substances and degradation products	Not more than 0.4 per cent in total of specified drug substance related impurities. * Not more than 0.4 per cent in total of unspecified drug substance related impurities. Less than 0.10 per cent of any individual unspecified drug substance related impurity. * limits for individual specified drug substance related impurities: Not more than 0.2 % of 16α-hydroxyprednisolone Not more than 0.1 % of D-homobudesonide Not more than 0.1 % of 21-dehydrobudesonide Not more than 0.1 % of 14,15-dehydrobudesonide
11	Budesonide	98.0 - 102.0 per cent (m/m).
12	Microbial quality	Total aerobic microbial count ≤ 10 cfu/g. Total yeast and mold count ≤ 5 cfu/g. (The total content of 10 inhalers is tested in accordance with USP under Microbial limits test <61>.)

ASTRA

SPECIFICATION

Date (Yr, Mo, Day)		Specification No.
91-04-25 Product Company DRACO Issued by Prepared by	RHINOCORT nasal spray 50 µg/dose, (1 mg/ml), 2.5 ml	21-221-66/4 Supersedes Specification No. 21-221-66/3

	Description	A white to off-white, viscous, thixotropic suspension. Glass bottle provided with a pump spray equipment. Density: 1.02 g/cm^3
		Requirements
1	Appearance	A white to off-white, viscous, thixotropic suspension.
2	Weight of dose	The average dose weight from a single bottle 43.5 - 58.5 mg. (5 doses per bottle, 10 bottles). If one bottle is outside the limits, test 10 more bottles. All of the additional bottles must be within the limits. The average dose weight from all bottles 46.0 - 56.0 mg.
3	pH	4.0 - 4.8
4	Budesonide (identity)	Positive identity.
5	Budesonide	Release: 0.95 - 1.05 mg/ml Shelf life: 0.90 - 1.10 mg/ml
6	Potassium sorbate	Release: 1.08 - 1.32 mg/ml Shelf life: 0.60 - 1.32 mg/ml
7	Microbiological condition	Not more than 10^2 microorganisms per gram. No detectable pathogenic microorganisms. No increase in the number of microorganisms during storage.

Guidance for Industry

Sterility Requirement for Aqueous-Based Drug Products for Oral Inhalation — Small Entity Compliance Guide

Additional copies are available from:
Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

November 2001
Small Entity Compliance Guides

Guidance for Industry[1]

Sterility Requirement for Aqueous-Based Drug Products for Oral Inhalation — Small Entity Compliance Guide

I. INTRODUCTION

This small entity compliance guide is one of a series of guidance documents prepared in accordance with section 212 of the Small Business Regulatory Fairness Act (Public Law 104-121). The guidances are intended to explain the actions small entities are required to take to comply with rules for which the Agency prepared a final regulatory flexibility analysis.

This guidance restates in plain language the legal requirements set forth in the current regulation requiring that all prescription and over-the counter (OTC) aqueous-based drug products for oral inhalation be manufactured sterile. FDA issued a final rule, published in the *Federal Register* of May 26, 2000 (65 FR 34082), in response to reports of adverse drug experiences from contaminated nonsterile inhalation drug products and recalls of these products. FDA issued the final rule after considering all comments on the proposed rule, which was published in the *Federal Register* of October 11, 1991 (56 FR 51354).

II. SUMMARY OF THE REGULATION

In the final rule, FDA amended its regulations governing specific classes of drug products by adding new § 200.51 (21 CFR 200.51). Section 200.51 requires that all aqueous-based drug products for oral inhalation be manufactured sterile as of the effective date of the rule. Manufacturers must also comply with § 211.113(b) (21 CFR 211.113(b)), which requires them to establish and follow appropriate written procedures designed to prevent microbiological contamination of any product manufactured sterile, including validation of any sterilization process used. Manufacturers must be in compliance with the final rule as of its effective date, May 27, 2002.

[1] This small business compliance guide was developed by the Office of Regulatory Policy in the Center for Drug Evaluation and Research, FDA.

III. QUESTIONS AND ANSWERS

Question: **Is the product I manufacture subject to this rule?**
Answer: If you manufacture an aqueous-based oral inhalation drug product, your drug product is subject to this rule and must be manufactured sterile. The rule applies to drug products packaged in both single-dose and multiple-use primary packaging. ***Nasal spray drug products and pressurized metered-dose inhalers are not subject to this rule.***

Question: **I manufacture an aqueous-based oral inhalation drug product that is packaged in single-dose primary packaging. Is my drug product subject to this rule?**
Answer: Yes, drug products packaged in both single-dose and multiple-use primary packaging are subject to this rule.

Question: **I manufacture an aqueous-based oral inhalation drug product that is a suspension. Is my drug product subject to this rule?**
Answer: Aqueous-based suspensions for oral inhalation are subject to this rule. However, if your suspension drug product is packaged in a pressurized metered-dose inhaler, it is not subject to the rule.

Question: **I currently manufacture a drug product that is subject to this rule and is not manufactured sterile. What must I do to comply with this rule?**
Answer: You must submit a supplemental new drug application (NDA) or a supplemental abbreviated new drug application (ANDA) to establish the sterility of your drug product. Your supplemental application must be submitted to FDA no later than May 27, 2002.

Question: **I currently have an NDA or ANDA pending for a nonsterile aqueous-based drug product for oral inhalation with FDA. What must I do to comply with this rule?**
Answer: If your NDA or ANDA was under review by FDA between May 26, 2000, and May 27, 2002, your application may be approved if it is otherwise approvable and you agree to establish the sterility of the drug product in a supplemental application by May 27, 2002. On or after May 27, 2002, FDA will refuse to approve an NDA or ANDA for your drug product if you have not established the sterility of the product.

Question: **I plan to manufacture a new drug product that is subject to this rule. What must I do to comply with this rule?**
Answer: The NDA or ANDA you submit to FDA must establish the sterility of your drug product.

Question: **When must I be in compliance with this rule?**

Answer: You must be in compliance with this rule no later than May 27, 2002. On or after May 27, 2002, you are prohibited from introducing or delivering for introduction into interstate commerce any nonsterile aqueous-based drug products for oral inhalation except for those drug products marketed in pressurized metered-dose inhalers or as nasal sprays.

Question: **What will happen if I fail to comply with this rule by May 27, 2002?**

Answer: If you fail to comply with this rule by May 27, 2002, your drug product will be found to be adulterated under section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 351 (a)(2)(B)) and misbranded under section 502(j) of the Act (21 U.S.C. 352(j)) and may be subject to regulatory action. In addition, the Agency will refuse to approve a new or abbreviated application for a drug product that fails to comply with this rule, under section 505(d)(1), (d)(2), (d)(3), and (j)(4)(A) of the Act (21 U.S.C. 355(d)(1), (d)(2), (d)(3), and (j)(4)(A)).

Question: **If I have questions about whether the drug product I manufacture is subject to this rule, how to comply with the rule, or any related issues, whom should I contact at FDA?**

Answer: You should contact the Assistant Director for Microbiology, Office of New Drug Chemistry, at the Center for Drug Evaluation and Research (HFD-805), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-7340.

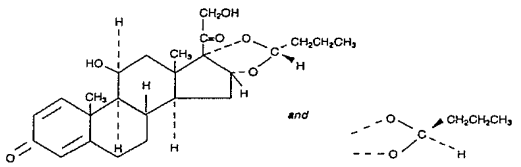
Pulmicort Respules®
(budesonide inhalation suspension)
0.25 mg, 0.5 mg, and 1 mg

Rx only

For inhalation use via compressed air driven jet nebulizers only (not for use with ultrasonic devices). Not for injection. Read patient instructions before using.

DESCRIPTION

Budesonide, the active component of PULMICORT RESPULES®, is a corticosteroid designated chemically as (RS)-11β, 16α, 17, 21-tetrahydroxypregna-1, 4-diene-3, 20-dione cyclic 16, 17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is $C_{25}H_{34}O_6$ and its molecular weight is 430.5. Its structural formula is:



Budesonide is a white to off-white, tasteless, odorless powder that is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform. Its partition coefficient between octanol and water at pH 7.4 is 1.6×10^3.

PULMICORT RESPULES is a sterile suspension for inhalation via jet nebulizer and contains the active ingredient budesonide (micronized), and the inactive ingredients disodium edetate, sodium chloride, sodium citrate, citric acid, polysorbate 80, and Water for Injection. Three dose strengths are available in single-dose ampules (Respules™ ampules): 0.25 mg, 0.5 mg, and 1 mg per 2 mL RESPULES ampule. For PULMICORT RESPULES, like all other nebulized treatments, the amount delivered to the lungs will depend on patient factors, the jet nebulizer utilized, and compressor performance. Using the Pari-LC-Jet Plus Nebulizer/Pari Master compressor system, under *in vitro* conditions, the mean delivered dose at the mouthpiece (% nominal dose) was approximately 17% at a mean flow rate of 5.5 L/min. The mean nebulization time was 5 minutes or less. PULMICORT RESPULES should be administered from jet nebulizers at adequate flow rates, via face masks or mouthpieces (see DOSAGE AND ADMINISTRATION).

CLINICAL PHARMACOLOGY

Mechanism of Action

Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay.

The activity of PULMICORT RESPULES is due to the parent drug, budesonide. In glucocorticoid receptor affinity studies, the 22R form was two times as active as the 22S epimer. *In vitro* studies indicated that the two forms of budesonide do not interconvert.

The precise mechanism of corticosteroid actions on inflammation in asthma is not well known. Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (eg, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (eg, histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic- and non-allergic-mediated inflammation. The anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Studies in asthmatic patients have shown a favorable ratio between topical anti-inflammatory activities and systemic corticosteroid effects over a wide dose range of inhaled budesonide in a variety of formulations and delivery systems including an inhalation-driven, multi-dose dry powder inhaler and the inhalation suspension for nebulization. This is explained by a combination of a relatively high local anti-inflammatory effect, extensive first pass hepatic degradation of orally absorbed drug (85-95%) and the low potency of metabolites (see below).

Pharmacokinetics

Absorption: In asthmatic children 4-6 years of age, the total absolute bioavailability (ie, lung + oral) following administration of PULMICORT RESPULES via jet nebulizer was approximately 6% of the labeled dose.

In children, a peak plasma concentration of 2.6 nmol/L was obtained approximately 20 minutes after nebulization of a 1 mg dose. Systemic exposure, as measured by AUC and C_{max}, is similar for young children and adults after inhalation of the same dose of PULMICORT RESPULES.

Distribution: In asthmatic children 4-6 years of age, the volume of distribution at steady-state of budesonide was 3 L/kg, approximately the same as in healthy adults. Budesonide is 85-90% bound to plasma proteins, the degree of binding being constant over the concentration range (1-100 nmol/L) achieved with, and exceeding, recommended doses. Budesonide showed little or no binding to corticosteroid-binding globulin. Budesonide rapidly equilibrated with red blood cells in a concentration independent manner with a blood/plasma ratio of about 0.8.

Metabolism: In vitro studies with human liver homogenates have shown that budesonide is rapidly and extensively metabolized. Two major metabolites formed via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4) catalyzed biotransformation have been isolated and identified as 16α-hydroxyprednisolone and 6β-hydroxybudesonide. The corticosteroid activity of each of these two metabolites is less than 1% of that of the parent compound. No qualitative difference between the *in vitro* and *in vivo* metabolic patterns has been detected. Negligible metabolic inactivation was observed in human lung and serum preparations.

Excretion/Elimination: Budesonide is primarily cleared by the liver. Budesonide is excreted in urine and feces in the form of metabolites. In adults, approximately 60% of an intravenous radiolabeled dose was recovered in the urine. No unchanged budesonide was detected in the urine.

In asthmatic children 4-6 years of age, the terminal half-life of budesonide after nebulization is 2.3 hours, and the systemic clearance is 0.5 L/min, which is approximately 50% greater than in healthy adults after adjustment for differences in weight.

Special Populations: No differences in pharmacokinetics due to race, gender, or age have been identified.

Hepatic Insufficiency: Reduced liver function may affect the elimination of corticosteroids. The pharmacokinetics of budesonide were affected by compromised liver function as evidenced by a doubled systemic availability after oral ingestion. The intravenous pharmacokinetics of budesonide were, however, similar in cirrhotic patients and in healthy adults.

Nursing Mothers: The disposition of budesonide when delivered by inhalation from a dry powder inhaler at doses of 200 or 400 mcg twice daily for at least 3 months was studied in eight lactating women with asthma from 1 to 6 months postpartum. Systemic exposure to budesonide in these women appears to be comparable to that in non-lactating women with asthma from other studies. Breast milk obtained over eight hours post-dose revealed that the maximum concentration of budesonide for the 400 and 800 mcg doses was 0.39 and 0.78 nmol/L, respectively, and occurred within 45 minutes after dosing. The estimated oral daily dose of budesonide from breast milk to the infant is approximately 0.007 and 0.014 mcg/kg/day for the two dose regimens used in this study, which represents approximately 0.3% to 1% of the dose inhaled by the mother. Budesonide levels in plasma samples obtained from five infants at about 90 minutes after breast-feeding (and about 140 minutes after drug administration to the mother) were below quantifiable levels (<0.02 nmol/L in four infants and <0.04 nmol/L in one infant) (see PRECAUTIONS, Nursing Mothers).

Pharmacodynamics

The therapeutic effects of conventional doses of orally inhaled budesonide are largely explained by its direct local action on the respiratory tract. To confirm that systemic absorption is not a significant factor in the clinical efficacy of inhaled budesonide, a clinical study in adult patients with asthma was performed comparing 400 mcg budesonide administered via a pressurized metered dose inhaler with a tube spacer to 1400 mcg of oral budesonide and placebo. The study demonstrated the efficacy of inhaled budesonide but not orally ingested budesonide despite comparable systemic levels.

Improvement in the control of asthma symptoms following inhalation of PULMICORT RESPULES can occur within 2-8 days of beginning treatment, although maximum benefit may not be achieved for 4-6 weeks.

Budesonide administered via a dry powder inhaler has been shown in various challenge models (including histamine, methacholine, sodium metabisulfite, and adenosine monophosphate) to decrease bronchial hyperresponsiveness in asthmatic patients. The clinical relevance of these models is not certain.

Pre-treatment with budesonide administered as 1600 mcg daily (800 mcg twice daily) via a dry powder inhaler for 2 weeks reduced the acute (early-phase reaction) and delayed (late-phase reaction) decrease in FEV_1 following inhaled allergen challenge.

The effects of PULMICORT RESPULES on the hypothalamic-pituitary-adrenal (HPA) axis were studied in three, 12-week, double-blind, placebo-controlled studies in 293 pediatric patients, 6 months to 8 years of age, with persistent asthma. For most patients, the ability to increase cortisol production in response to stress, as assessed by the short cosyntropin (ACTH) stimulation test, remained intact with PULMICORT RESPULES treatment at recommended doses. In the subgroup of children age 6 months to 2 years (n=21) receiving a total daily dose of PULMICORT RESPULES equivalent to 0.25 mg (n=5), 0.5 mg (n=5), 1 mg (n=8), or placebo (n=3), the mean change from baseline in ACTH-stimulated cortisol levels showed a decline in peak stimulated cortisol at 12 weeks compared to an increase in the placebo group. These mean differences were not statistically significant compared to placebo. Another 12-week study in 141 pediatric patients 6 to 12 months of age with mild to moderate asthma or recurrent/persistent wheezing was conducted. All patients were randomized to receive either 0.5 mg or 1 mg of PULMICORT RESPULES or placebo once daily. A total of 28, 17, and 31 patients in the PULMICORT RESPULES 0.5 mg, 1 mg, and placebo arms respectively, had an evaluation of serum cortisol levels post-ACTH stimulation both at baseline and at the end of the study. The mean change from baseline to Week 12 ACTH-stimulated minus basal plasma cortisol levels did not indicate adrenal suppression in patients treated with PULMICORT RESPULES versus placebo. However, 7 patients in this study (4 of whom received PULMICORT RESPULES 0.5 mg, 2 of whom received PULMICORT RESPULES 1 mg and 1 of whom received placebo) showed a shift from normal baseline stimulated cortisol level (≥500 nmol/L) to a subnormal level (<500 nmol/L) at Week 12. In 4 of these patients receiving PULMICORT RESPULES, the cortisol values were near the cutoff value of 500 nmol/L.

The effects of PULMICORT RESPULES at doses of 0.5 mg twice daily, and 1 mg and 2 mg twice daily (2 times and 4 times the highest recommended total daily dose, respectively) on 24-hour urinary cortisol excretion were studied in 18 patients between 6 to 15 years of age with persistent asthma in a cross-over study design (4 weeks of treatment per dose level). There was a dose-related decrease in urinary cortisol excretion at 2 and 4 times the recommended daily dose. The two higher doses of PULMICORT RESPULES (1 and 2 mg twice daily) showed statistically significantly reduced (43-52%) urinary cortisol excretion compared to the run-in period. The highest recommended dose of PULMICORT RESPULES, 1 mg total daily dose, did not show statistically significantly reduced urinary cortisol excretion compared to the run-in period.

PULMICORT RESPULES, like other inhaled corticosteroid products, may impact the HPA axis, especially in susceptible individuals, in younger children, and in patients given high doses for prolonged periods.

CLINICAL TRIALS

Three double-blind, placebo-controlled, parallel group, randomized U.S. clinical trials of 12-weeks duration each were conducted in 1018 pediatric patients, 6 months to 8 years of age, with persistent asthma of varying disease duration (2 to 107 months) and severity. Doses of 0.25 mg, 0.5 mg, and 1 mg administered either once or twice daily were compared to placebo to provide information about appropriate dosing to cover a range of asthma severity. A Pari-LC-Jet Plus Nebulizer (with a face mask or mouthpiece) connected to a Pari Master compressor was used to deliver PULMICORT RESPULES to patients in the 3 U.S. controlled clinical trials. The co-primary endpoints were nighttime and daytime asthma symptom scores (0-3 scale). Each of the five doses discussed below were studied in one or two, but not all three of the U.S. studies.

Results of the 3 controlled clinical trials for recommended dosages of budesonide inhalation suspension (0.25 mg to 0.5 mg once or twice daily, or 1 mg once daily, up to a total daily dose of 1 mg) in 946 patients, 12 months to 8 years of age, are presented below. Compared to placebo, PULMICORT RESPULES significantly decreased both nighttime and daytime symptom scores of asthma at doses of 0.25 mg once daily (one study), 0.25 mg twice daily, and 0.5 mg twice daily. PULMICORT RESPULES significantly decreased either nighttime or daytime symptom scores, but not both, at doses of 1 mg once daily, and 0.5 mg once daily (one study). Symptom reduction in response to PULMICORT RESPULES occurred across gender and age. PULMICORT RESPULES significantly reduced the need for bronchodilator therapy at all the doses studied.

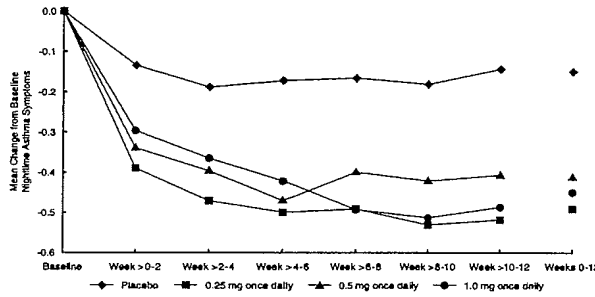
Improvements in lung function were associated with PULMICORT RESPULES in the subgroup of patients capable of performing lung function testing. Significant improvements were seen in FEV_1 [PULMICORT RESPULES 0.5 mg once daily and 1 mg once daily (one study); 0.5 mg twice daily] and morning PEF [PULMICORT RESPULES 1 mg once daily (one study); 0.25 mg twice daily; 0.5 mg twice daily] compared to placebo.

A numerical reduction in nighttime and daytime symptom scores (0-3 scale) of asthma was observed within 2-8 days, although maximum benefit was not achieved for 4-6 weeks after starting treatment. The reduction in nighttime and daytime asthma symptom scores was maintained throughout the 12 weeks of the double-blind trials.

Patients Not Receiving Inhaled Corticosteroid Therapy

The efficacy of PULMICORT RESPULES at doses of 0.25 mg, 0.5 mg, and 1 mg once daily was evaluated in 344 pediatric patients, 12 months to 8 years of age, with mild to moderate persistent asthma (mean baseline nighttime asthma symptom scores of the treatment groups ranged from 1.07 to 1.34) who were not well controlled by bronchodilators alone. The changes from baseline to Weeks 0-12 in nighttime asthma symptom scores are shown in Figure 1. Nighttime asthma symptom scores improved significantly in the patients treated with PULMICORT RESPULES compared to placebo. Similar improvements were also observed for daytime asthma symptom scores.

Figure 1: A 12-Week Trial in Pediatric Patients Not on Inhaled Corticosteroid Therapy Prior to Study Entry.

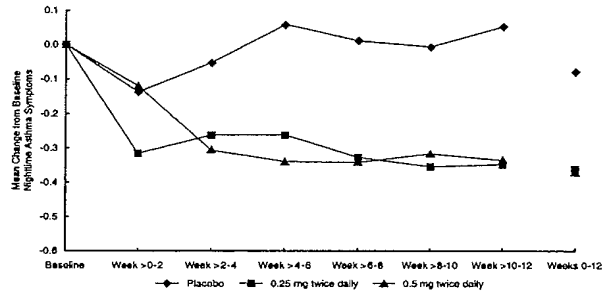


Patients Previously Maintained on Inhaled Corticosteroids

The efficacy of PULMICORT RESPULES at doses of 0.25 mg and 0.5 mg twice daily was evaluated in 133 pediatric asthma patients, 4 to 8 years of age, previously maintained on inhaled corticosteroids (mean FEV_1 79.5% predicted; mean baseline nighttime asthma symptom scores of the treatment groups ranged from 1.04 to 1.18; mean baseline dose of beclomethasone dipropionate of 265 mcg/day, ranging between 42 to 1008 mcg/day; mean baseline dose of triamcinolone acetonide of 572 mcg/day, ranging between 200 to 1200 mcg/day). The changes from baseline to Weeks 0-12 in nighttime asthma symptom scores are shown in Figure 2. Nighttime asthma symptom scores were significantly improved in patients treated with PULMICORT RESPULES compared to placebo. Similar improvements were also observed for daytime asthma symptom scores.

PULMICORT RESPULES at a dose of 0.5 mg twice daily significantly improved FEV_1, and both doses (0.25 mg and 0.5 mg twice daily) significantly increased morning PEF, compared to placebo.

Figure 2: A 12-Week Trial in Pediatric Patients Previously Maintained on Inhaled Corticosteroid Therapy Prior to Study Entry.



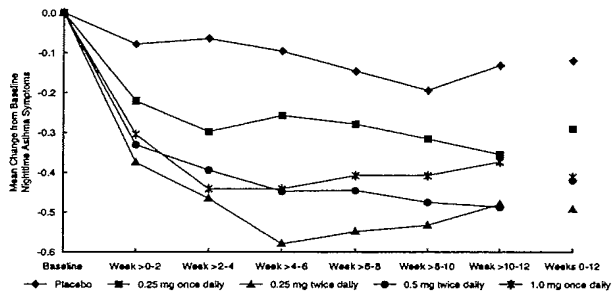
Patients Receiving Once-Daily or Twice-Daily Dosing

The efficacy of PULMICORT RESPULES at doses of 0.25 mg once daily, 0.25 mg twice daily, 0.5 mg twice daily, and 1 mg once daily, was evaluated in 469 pediatric patients 12 months to 8 years of age (mean baseline nighttime asthma symptom scores of the treatment groups ranged from 1.13 to 1.31). Approximately 70% were not previously receiving inhaled corticosteroids. The changes from baseline to Weeks 0-12 in nighttime asthma symptom scores are shown in Figure 3. PULMICORT RESPULES at doses of 0.25 mg and 0.5 mg twice daily, and 1 mg once daily, significantly improved nighttime asthma symptom scores compared to placebo. Similar improvements were also observed for daytime asthma symptom scores.

PULMICORT RESPULES at a dose of 0.5 mg twice daily significantly improved FEV_1, and at doses of 0.25 mg and 0.5 mg twice daily and 1 mg once daily significantly improved morning PEF, compared to placebo.

The evidence supports the efficacy of the same nominal dose of PULMICORT RESPULES administered on either a once-daily or twice-daily schedule. However, when all measures are considered together, the evidence is stronger for twice-daily dosing (see DOSAGE AND ADMINISTRATION).

Figure 3: A 12-Week Trial in Pediatric Patients Either Maintained on Bronchodilators Alone or Inhaled Corticosteroid Therapy Prior to Study Entry.



INDICATIONS

PULMICORT RESPULES is indicated for the maintenance treatment of asthma and as prophylactic therapy in children 12 months to 8 years of age.

PULMICORT RESPULES is NOT indicated for the relief of acute bronchospasm.

PULMICORT RESPULES® (budesonide inhalation suspension) 0.25 mg, 0.5 mg, and 1 mg

CONTRAINDICATIONS

PULMICORT RESPULES is contraindicated as the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to budesonide or any of the ingredients of this preparation contraindicates the use of PULMICORT RESPULES.

WARNINGS

Particular care is needed for patients who are transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA)-axis function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn.

During this period of HPA-axis suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although PULMICORT RESPULES may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of corticosteroid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instructions. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to PULMICORT RESPULES. Lung function (FEV_1 or AM PEF), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to PULMICORT RESPULES may unmask allergic or other immunologic conditions previously suppressed by the systemic corticosteroid therapy, eg, rhinitis, conjunctivitis, eosinophilic conditions, eczema, and arthritis (see DOSAGE AND ADMINISTRATION).

Patients who are on drugs which suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible pediatric patients or adults on immunosuppressant doses of corticosteroids. In pediatric or adult patients who have not had these diseases, or who have not been properly vaccinated, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known.

The clinical course of chicken pox or measles infection in patients on inhaled corticosteroids has not been studied. However, a clinical study has examined the immune responsiveness of asthma patients 12 months to 8 years of age who were treated with PULMICORT RESPULES (see PRECAUTIONS, Pediatric Use).

If a patient on immunosuppressant doses of corticosteroids is exposed to chicken pox, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered.

PULMICORT RESPULES is not a bronchodilator and is not indicated for the rapid relief of acute bronchospasm or other acute episodes of asthma.

As with other inhaled asthma medications, bronchospasm, with an immediate increase in wheezing, may occur after dosing. If acute bronchospasm occurs following dosing with PULMICORT RESPULES, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with PULMICORT RESPULES should be discontinued and alternate therapy instituted.

Patients should be instructed to contact their physician immediately when episodes of asthma not responsive to their usual doses of bronchodilators occur during treatment with PULMICORT RESPULES.

PRECAUTIONS

General

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, eg, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function (see DOSAGE AND ADMINISTRATION).

Because budesonide is absorbed into the circulation and may be systemically active, particularly at higher doses, suppression of HPA function may be associated when PULMICORT RESPULES is administered at doses exceeding those recommended (see DOSAGE AND ADMINISTRATION), or when the dose is not titrated to the lowest effective dose. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing PULMICORT RESPULES.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with PULMICORT RESPULES should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients post-operatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism, reduced bone mineral density, and adrenal suppression may appear in a small number of patients, particularly at higher doses. If such changes occur, PULMICORT RESPULES should be reduced slowly, consistent with accepted procedures for management of asthma symptoms and for tapering of systemic corticosteroids.

Orally inhaled corticosteroids, including budesonide, may cause a reduction in growth velocity when administered to pediatric patients. A reduction in growth velocity may occur as a result of inadequate control of asthma or from use of corticosteroids for treatment. The potential effects of prolonged treatment on growth velocity should be weighed against the clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including PULMICORT RESPULES, each patient should be titrated to his/her lowest effective dose (see PRECAUTIONS, Pediatric Use).

Although patients in clinical trials have received PULMICORT RESPULES on a continuous basis for periods of up to 1 year, the long-term local and systemic effects of PULMICORT RESPULES in human subjects are not completely known. In particular, the effects resulting from chronic use of PULMICORT RESPULES on developmental or immunological processes in the mouth, pharynx, trachea, and lung are unknown.

In clinical trials with PULMICORT RESPULES, localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. The incidences of localized infections of *Candida albicans* were similar between the placebo and PULMICORT RESPULES treatment groups. If these infections develop, they may require treatment with appropriate antifungal therapy and/or discontinuance of treatment with PULMICORT RESPULES.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract, untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids.

Information for Patients

Patients being treated with PULMICORT RESPULES should receive the following information and instructions. This information is intended to aid the patient in the safe and effective use of the medication. It is not a disclosure of all possible adverse or intended effects. For instructions on the proper use of PULMICORT RESPULES and to attain the maximum improvement in asthma symptoms, the patient or the parent/guardian of the patient should receive, read, and follow the accompanying patient information and instructions carefully.

- Patients should take PULMICORT RESPULES at regular intervals once or twice a day as directed, since its effectiveness depends on regular use. The patient should not alter the prescribed dosage unless advised to do so by the physician.
- The effects of mixing PULMICORT RESPULES with other nebulizable medications have not been adequately assessed. PULMICORT RESPULES should be administered separately in the nebulizer.
- PULMICORT RESPULES is not a bronchodilator, and its use is not intended to treat acute life-threatening episodes of asthma.
- PULMICORT RESPULES should be administered with a jet nebulizer connected to a compressor with an adequate air flow, equipped with a mouthpiece or suitable face mask. The face mask should be properly adjusted to optimize delivery and to avoid exposing the eyes to the nebulized medication (see DOSAGE AND ADMINISTRATION).
- Ultrasonic nebulizers are not suitable for the adequate administration of PULMICORT RESPULES and, therefore, are not recommended (see DOSAGE AND ADMINISTRATION).
- Rinsing the mouth with water after each treatment may decrease the risk of development of local candidiasis. Corticosteroid effects on the skin can be avoided if the face is washed after the use of a face mask.
- Improvement in asthma control following treatment with PULMICORT RESPULES can occur within 2-8 days of beginning treatment, although maximum benefit may not be achieved for 4-6 weeks after starting treatment. If the asthma symptoms do not improve in that time frame, or if the condition worsens, the patient or the patient's parent/guardian should be instructed not to increase the dosage, but to contact the physician.
- Patients should not stop the use of PULMICORT RESPULES abruptly without consulting with their prescribing physician.
- Patients whose chronic systemic corticosteroids have been reduced or withdrawn should be instructed to carry a warning card indicating that they may need supplemental systemic corticosteroids during periods of stress or an asthma attack that does not respond to bronchodilators.
- As always, care should be taken to avoid exposure to persons with chicken pox and measles. If exposure to such a person occurs, and the child has not had chicken pox or been properly vaccinated, a physician should be consulted without delay (see WARNINGS, and PRECAUTIONS, Pediatric Use).
- Long-term use of inhaled corticosteroids, including budesonide, may increase the risk of some eye problems (cataracts or glaucoma). Regular eye examinations should be considered.
- Patients or their parents/guardians considering use of PULMICORT RESPULES should consult with their physician if they are allergic to budesonide or any other orally inhaled corticosteroid.
- Physicians should be informed of other medications patients are taking as PULMICORT RESPULES may not be suitable in some circumstances and the physician may wish to use a different medicine.
- PULMICORT RESPULES should be stored upright at controlled room temperature 20–25°C (68–77°F) and protected from light. PULMICORT RESPULES should not be refrigerated or frozen.
- When an aluminum foil envelope has been opened, the shelf life of the unused RESPULES ampules is two weeks when protected from light. The date the envelope was opened should be recorded on the back of the envelope in the space provided.
- After opening the aluminum foil envelope, the unused RESPULES ampules should be returned to the envelope to protect them from light. Any individually opened RESPULES ampules must be used promptly.
- For proper usage of PULMICORT RESPULES and to attain maximum improvement, the accompanying Patient's Instructions for Use should be read and followed.

Drug Interactions

In clinical studies, concurrent administration of budesonide and other drugs commonly used in the treatment of asthma has not resulted in an increased frequency of adverse events. The main route of metabolism of budesonide, as well as other corticosteroids, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a potent inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of other known inhibitors of CYP3A4 (eg, itraconazole, clarithromycin, erythromycin, etc.) may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Care should be exercised when budesonide is coadministered with long-term ketoconazole and other known CYP3A4 inhibitors. Omeprazole did not have effects on the pharmacokinetics of oral budesonide, while cimetidine, primarily an inhibitor of CYP1A2, caused a slight decrease in budesonide clearance and a corresponding increase in its oral bioavailability.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies were conducted in rats and mice using oral administration to evaluate the carcinogenic potential of budesonide.

In a two-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m^2 basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m^2 basis). In two additional two-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m^2 basis). However, in the male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m^2 basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings.

In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m^2 basis).

Budesonide was not mutagenic or clastogenic in six different test systems: Ames *Salmonella*/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in *Drosophila melanogaster*, and DNA repair analysis in rat hepatocyte culture.

In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). However, it caused a decrease in prenatal viability and viability in the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg and above (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). No such effects were noted at 5 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis).

PULMICORT RESPULES® (budesonide inhalation suspension) 0.25 mg, 0.5 mg, and 1 mg

Pregnancy

Teratogenic Effects: Pregnancy Category B—As with other corticosteroids, budesonide was teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weights, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg in rabbits (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) and 500 mcg/kg in rats (approximately 4 times the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 250 mcg/kg (approximately 2 times the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis).

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

Studies of pregnant women, however, have not shown that inhaled budesonide increases the risk of abnormalities when administered during pregnancy. The results from a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-1997 (ie, Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry) indicate no increased risk for congenital malformations from the use of inhaled budesonide during early pregnancy. Congenital malformations were studied in 2014 infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 10–12 weeks after the last menstrual period), the period when most major organ malformations occur. The rate of recorded congenital malformations was similar compared to the general population rate (3.8 % vs. 3.5%, respectively). In addition, after exposure to inhaled budesonide, the number of infants born with orofacial clefts was similar to the expected number in the normal population (4 children vs. 3.3, respectively).

These same data were utilized in a second study bringing the total to 2534 infants whose mothers were exposed to inhaled budesonide. In this study, the rate of congenital malformations among infants whose mothers were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%).

Despite the animal findings, it would appear that the possibility of fetal harm is remote if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, PULMICORT RESPULES should be used during pregnancy only if clearly needed.

Non-teratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers

Budesonide, like other corticosteroids, is secreted in human milk. Data with budesonide delivered via dry powder inhaler indicates that the total daily oral dose of budesonide in breast milk to the infant is approximately 0.3% to 1% of the dose inhaled by the mother (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Nursing Mothers). No studies have been conducted in breastfeeding women with PULMICORT RESPULES; however, the dose of budesonide available to the infant in breast milk, as a percentage of the maternal dose, would be expected to be similar. PULMICORT RESPULES should be used in nursing women only if clinically appropriate. Prescribers should weigh the known benefits of breastfeeding for the mother and the infant against the potential risks of minimal budesonide exposure in the infant.

Pediatric Use

Safety in children six months to 12 months of age has been evaluated. Safety and effectiveness in children 12 months to 8 years of age have been established (see CLINICAL PHARMACOLOGY, Pharmacodynamics, CLINICAL TRIALS and ADVERSE REACTIONS).

A 12-week study in 141 pediatric patients 6 to 12 months of age with mild to moderate asthma or recurrent/persistent wheezing was conducted. All patients were randomized to receive either 0.5 mg or 1 mg of PULMICORT RESPULES or placebo once daily. Adrenal axis function was assessed with an ACTH stimulation test at the beginning and end of the study, and mean changes from baseline in this variable did not indicate adrenal suppression in patients who received PULMICORT RESPULES versus placebo. However, on an individual basis, 7 patients in this study (6 in the PULMICORT RESPULES treatment arms and 1 in the placebo arm) experienced a shift from having a normal baseline stimulated cortisol level to having a subnormal level at Week 12 (see CLINICAL PHARMACOLOGY, Pharmacodynamics). Pneumonia was observed more frequently in patients treated with PULMICORT RESPULES than in patients treated with placebo, (N = 2, 1, and 0) in the PULMICORT RESPULES 0.5 mg, 1 mg, and placebo groups, respectively.

A dose dependent effect on growth was also noted in this 12-week trial. Infants in the placebo arm experienced an average growth of 3.7 cm over 12 weeks compared with 3.5 cm and 3.1 cm in the PULMICORT RESPULES 0.5 mg and 1 mg arms respectively. This corresponds to estimated mean (95% CI) reductions in 12-week growth velocity between placebo and PULMICORT RESPULES 0.5 mg of 0.2 cm (-0.6 to 1.0) and between placebo and PULMICORT RESPULES 1 mg of 0.6 cm (-0.2 to 1.4). These findings support that the use of PULMICORT RESPULES in infants 6 to 12 months of age may result in systemic effects and are consistent with findings of growth suppression in other studies with inhaled corticosteroids.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. In these studies, the mean reduction in growth velocity was approximately one centimeter per year (range 0.3 to 1.8 cm per year) and appears to be related to dose and duration of exposure. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA)-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

In a study of asthmatic children 5-12 years of age, those treated with budesonide administered via a dry powder inhaler 200 mcg twice daily (n=311) had a 1.1-centimeter reduction in growth compared with those receiving placebo (n=418) at the end of one year; the difference between these two treatment groups did not increase further over three years of additional treatment. By the end of four years, children treated with the budesonide dry powder inhaler and children treated with placebo had similar growth velocities. Conclusions drawn from this study may be confounded by the unequal use of corticosteroids in the treatment groups and inclusion of data from patients attaining puberty during the course of the study.

The growth of pediatric patients receiving inhaled corticosteroids, including PULMICORT RESPULES, should be monitored routinely (eg, via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks and benefits associated with alternative therapies. To minimize the systemic effects of inhaled corticosteroids, including PULMICORT RESPULES, each patient should be titrated to his/her lowest effective dose.

An open-label non-randomized clinical study examined the immune responsiveness of varicella vaccine in 243 asthma patients 12 months to 8 years of age who were treated with PULMICORT RESPULES 0.25 mg to 1 mg daily (n=151) or non-corticosteroid asthma therapy (n=92) (ie, beta$_2$-agonists, leukotriene receptor antagonists, cromones). The percentage of patients developing a seroprotective antibody titer of ≥5.0 (gpELISA value) in response to the vaccination was similar in patients treated with PULMICORT RESPULES (85%) compared to patients treated with non-corticosteroid asthma therapy (90%). No patient treated with PULMICORT RESPULES developed chicken pox as a result of vaccination.

Geriatric Use

Of the 215 patients in 3 clinical trials of PULMICORT RESPULES in adult patients, 65 (30%) were 65 years of age or older, while 22 (10%) were 75 years of age or older. No overall differences in

Patient's Instructions for Use

2 mL ampules containing 0.25 mg, 0.5 mg, or 1 mg
FOR INHALATION ONLY.

Please read this leaflet carefully before taking PULMICORT RESPULES. It provides a summary of information about this medication. Following these instructions helps to ensure that you are using the medication correctly.

The medication named PULMICORT RESPULES is intended for inhalation use only with compressed air driven nebulizer systems, also known as jet nebulizers. Do not use with an ultrasonic nebulizer.

For further information, ask your doctor or pharmacist.

IMPORTANT POINTS TO REMEMBER ABOUT PULMICORT RESPULES

- Your doctor has prescribed PULMICORT RESPULES. It contains a medication called budesonide, which is a synthetic corticosteroid. It is important that your child take PULMICORT RESPULES using a compressed air driven jet nebulizer as instructed.
- Use this nebulizer therapy as directed at the same time each day, even during symptom-free periods. **DO NOT STOP TREATMENT OR REDUCE THE DOSE EVEN IF YOUR CHILD FEELS BETTER**, unless told to do so by your doctor.
- **DO NOT** let your child inhale more doses or use this medication more often than instructed.
- This medication is intended to help prevent and control asthma symptoms. It is NOT intended to provide rapid relief of breathing difficulties during an asthma attack.
- Your doctor may prescribe additional medication (such as bronchodilators) for emergency relief if an acute asthma attack occurs. Please contact your doctor if:
  - an asthma attack does not respond to the additional medication,
  - your child requires more of the additional medication than usual.
- If your child uses another medication by inhalation, consult your healthcare provider for instructions on when to use it in relation to using PULMICORT RESPULES.
- PULMICORT RESPULES has not been studied when mixed with other nebulizable medications. PULMICORT RESPULES should be given separately in the nebulizer.

BEFORE USING PULMICORT RESPULES

Tell your doctor before starting to take this medication if your child:

- Is allergic to budesonide or any other inhaled corticosteroid,
- Is taking any other medications,
- Has any infections,
- Has or had tuberculosis,
- Has osteoporosis,
- Has recently been around anyone with chicken pox or measles,
- Is planning to have surgery,
- Has been taking an oral corticosteroid medicine like prednisone. You may have to follow specific instructions to avoid health risks associated with stopping the use of these types of medicines.

In some circumstances, this medicine may not be suitable and your doctor may wish to prescribe a different medicine. Make sure that your doctor knows what other medicines your child is taking, including prescription and non-prescription medicines, as well as any vitamins or dietary and herbal supplements.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF PULMICORT RESPULES

As with all inhaled corticosteroids, you should be aware of the following side effects:

- **Increased wheezing right after taking PULMICORT RESPULES. Always have a short-acting bronchodilator medicine with you to treat sudden wheezing.** Short-acting bronchodilator medicines help to relax the muscles around the airways in your lungs. Wheezing happens when the muscles around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and cause death if not treated right away.
- **Immune system effects and a higher chance of infections.**
- **Eye problems including glaucoma and cataracts.** Eye examinations should be considered while using PULMICORT RESPULES.
- Your child's growth should be checked regularly while taking PULMICORT RESPULES because of the potential for slowed growth.

Based on clinical trials, the most common side effects reported by patients using PULMICORT RESPULES are:

- Respiratory infections
- Ear infections
- Runny nose

These are not all of the possible side effects of PULMICORT RESPULES. For more information, ask your doctor or pharmacist.

USING PULMICORT RESPULES

PULMICORT RESPULES should be used with a compressed air driven jet nebulizer following the manufacturer's instructions. The mist produced is then inhaled through either a mouthpiece or face mask. The treatment generally takes five to ten minutes. Treatment is complete when mist no longer comes out of the mouthpiece or face mask. The face mask should be properly adjusted to optimize delivery and to avoid exposing the eyes to the nebulized medication.

DOSAGE

Patients should take PULMICORT RESPULES at regular intervals once or twice a day, as directed, since its effectiveness depends on regular use.

Improvement in the control of asthma symptoms with PULMICORT RESPULES can occur within 2–8 days. It may take up to 4–6 weeks before maximum improvement is seen.

If your child misses a dose by more than several hours, just take the next regularly scheduled dose when it is due. **DO NOT DOUBLE** the dose.

HOW TO USE PULMICORT RESPULES

1. Assemble the nebulizer according to the instructions supplied by the manufacturer.
2. Open the sealed aluminum foil envelope along the dotted line and remove one (1) single-dose ampule from the strip (Figure 1). Record the date that you open the foil on the back of the envelope in the space provided.

   Place the unused Respules™ ampules remaining on the strip back into the aluminum foil envelope before storing. This will protect the medication from light. PULMICORT RESPULES should be stored upright at room temperature, 68–77°F (20–25°C). Do not refrigerate or freeze.

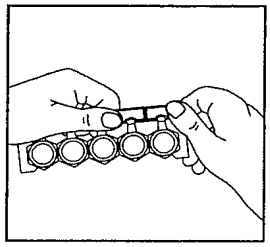


FIGURE 1

3. Gently shake the RESPULES ampule using a circular motion as shown in Figure 2.

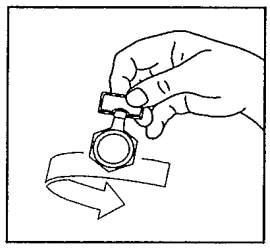


FIGURE 2

4. Hold the RESPULES ampule upright without squeezing and open by twisting off the top (Figure 3).
5. Place the open end of the RESPULES ampule into the nebulizer cup and slowly squeeze out all of the contents as shown in Figure 4.

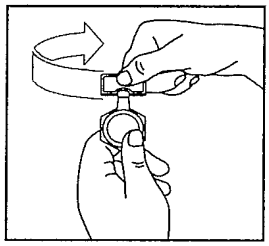


FIGURE 3

6. If using a face mask, make sure that the mask fits tightly so that the mist does not get into the child's eyes. Turn on the compressor to begin nebulizing the medication. Use the nebulizer as directed. Continue the treatment with PULMICORT RESPULES until mist is no longer coming out of the mouthpiece/face mask (usually about 5 to 10 minutes).
7. Throw away the empty RESPULES ampule. See the CLEANING OF EQUIPMENT and STORING YOUR PULMICORT RESPULES sections for additional information.

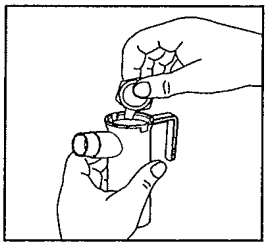


FIGURE 4

NOTE:

1. As with other inhaled corticosteroids, rinse your child's mouth with water after each dose to reduce the risk of developing thrush.
2. Wash your child's face after treatment to avoid possible skin irritation.

CLEANING OF EQUIPMENT

The nebulizer cup and the mouthpiece or the face mask should be cleaned according to the instructions supplied by the manufacturer.

STORING YOUR PULMICORT RESPULES

PULMICORT RESPULES should be stored in an upright position at temperatures between 68 and 77°F (20 and 25°C) in the aluminum foil envelope to protect from light. Do not freeze.

When the foil envelope is opened, the unused RESPULES ampules should be used within 2 weeks. After opening the aluminum foil package, the unused RESPULES ampules should be returned to the foil envelope to protect them from light. Any individually opened RESPULES ampule must be used promptly.

Remember to record the date you open the foil on the back of the envelope in the space provided.

Store PULMICORT RESPULES, like all medications, in a secure place out of the reach of children.

FURTHER INFORMATION ABOUT PULMICORT RESPULES

This leaflet does not contain the complete information about this medication. If you have any questions, you should ask your doctor or pharmacist.

You may want to read this leaflet again. Please DO NOT THROW IT AWAY until you have finished the medication.

REMEMBER: This medication has been prescribed for your child by your doctor. DO NOT give this medication to anyone else.

USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR DOCTOR.

If your child is exposed to chicken pox or measles, consult your doctor.

For additional information about PULMICORT RESPULES, please visit our website: pulmicortrespules.com or call the AstraZeneca Information Center, Monday through Friday, 8 am – 7 pm ET, excluding holidays:

1-800-236-9933

Manufactured for:
AstraZeneca LP, Wilmington, DE 19850
By: AstraZeneca AB, Södertälje, Sweden

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safety were observed between these patients and younger patients, and other reported clinical or medical surveillance experience has not identified differences in responses between the elderly and younger patients.

ADVERSE REACTIONS

The following adverse reactions were reported in pediatric patients treated with PULMICORT RESPULES.

The incidence of common adverse reactions is based on three double-blind, placebo-controlled, U.S. clinical trials in which 945 patients, 12 months to 8 years of age, (98 patients ≥12 months and <2 years of age; 225 patients ≥2 and <4 years of age; and 622 patients ≥4 and ≤8 years of age) were treated with PULMICORT RESPULES (0.25 to 1 mg total daily dose for 12 weeks) or vehicle placebo. The incidence and nature of adverse events reported for PULMICORT RESPULES was comparable to that reported for placebo. The following table shows the incidence of adverse events in U.S. controlled clinical trials, regardless of relationship to treatment, in patients previously receiving bronchodilators and/or inhaled corticosteroids. This population included a total of 605 male and 340 female patients.

Adverse Events with ≥ 3% Incidence Reported by Patients on PULMICORT RESPULES

Adverse Events	Vehicle Placebo (n=227) %	PULMICORT RESPULES Total Daily Dose		
		0.25 mg (n=178) %	0.5 mg (n=223) %	1 mg (n=317) %
Respiratory System Disorder				
Respiratory Infection	36	34	35	38
Rhinitis	9	7	11	12
Coughing	5	5	9	8
Resistance Mechanism Disorders				
Otitis Media	11	12	11	9
Viral Infection	3	4	5	3
Moniliasis	2	4	3	4
Gastrointestinal System Disorders				
Gastroenteritis	4	5	5	5
Vomiting	3	2	4	4
Diarrhea	2	4	4	2
Abdominal Pain	2	3	2	3
Hearing and Vestibular Disorders				
Ear Infection	4	2	4	5
Platelet, Bleeding, and Clotting Disorders				
Epistaxis	1	2	4	3
Vision Disorders				
Conjunctivitis	2	<1	4	2
Skin and Appendages Disorders				
Rash	3	<1	4	2

The table above shows all adverse events with an incidence of 3% or more in at least one active treatment group where the incidence was higher with PULMICORT RESPULES than with placebo.

The following adverse events occurred with an incidence of 3% or more in at least one PULMICORT RESPULES group where the incidence was equal to or less than that of the placebo group: fever, sinusitis, pain, pharyngitis, bronchospasm, bronchitis, and headache.

Incidence 1% to ≤3% (by body system)

The information below includes all adverse events with an incidence of 1 to ≤3%, in at least one PULMICORT RESPULES treatment group where the incidence was higher with PULMICORT RESPULES than with placebo, regardless of relationship to treatment.

Body as a whole: allergic reaction, chest pain, fatigue, flu-like disorder
Respiratory system: stridor
Resistance mechanisms: herpes simplex, external ear infection, infection
Central & peripheral nervous system: dysphonia, hyperkinesia
Skin & appendages: eczema, pustular rash, pruritus
Hearing & vestibular: earache
Vision: eye infection
Psychiatric: anorexia, emotional lability
Musculoskeletal system: fracture, myalgia
Application site: contact dermatitis
Platelet, bleeding & clotting: purpura
White cell and resistance: cervical lymphadenopathy

The incidence of reported adverse events was similar between the 447 PULMICORT RESPULES-treated (mean total daily dose 0.5 to 1 mg) and 223 conventional therapy-treated pediatric asthma patients followed for one year in three open-label studies.

Cases of growth suppression have been reported for inhaled corticosteroids including post-marketing reports for PULMICORT RESPULES (see PRECAUTIONS, Pediatric Use).

Less frequent adverse events (<1%) reported in the published literature, long-term, open-label clinical trials, or from worldwide marketing experience with any formulation of inhaled budesonide include: immediate and delayed hypersensitivity reactions including rash, contact dermatitis, urticaria, angioedema, and bronchospasm; symptoms of hypocorticism and hypercorticism; glaucoma, cataracts; psychiatric symptoms including depression, aggressive reactions, irritability, anxiety, and psychosis; and bone disorders including avascular necrosis of the femoral head and osteoporosis.

OVERDOSAGE

The potential for acute toxic effects following overdose of PULMICORT RESPULES is low. If inhaled corticosteroids are used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism or growth suppression may occur (see PRECAUTIONS).

In mice the minimal lethal inhalation dose was 100 mg/kg (approximately 410 or 120 times, respectively, the maximum recommended daily inhalation dose in adults or children on a mg/m² basis). In rats there were no deaths at an inhalation dose of 68 mg/kg (approximately 550 or 160 times, respectively, the maximum recommended daily inhalation dose in adults or children on a mg/m² basis). In mice the minimal oral lethal dose was 200 mg/kg (approximately 810 or 240 times, respectively, the maximum recommended daily inhalation dose in adults or children on a mg/m² basis). In rats, the minimal oral lethal dose was less than 100 mg/kg (approximately 810 or 240 times, respectively, the maximum recommended daily inhalation dose in adults or children on a mg/m² basis).

PULMICORT RESPULES® (budesonide inhalation suspension) 0.25 mg, 0.5 mg, and 1 mg

DOSAGE AND ADMINISTRATION

PULMICORT RESPULES is indicated for use in asthmatic patients 12 months to 8 years of age. PULMICORT RESPULES should be administered by the inhaled route via jet nebulizer connected to an air compressor. Individual patients will experience a variable onset and degree of symptom relief. Improvement in asthma control following inhaled administration of PULMICORT RESPULES can occur within 2-8 days of initiation of treatment, although maximum benefit may not be achieved for 4-6 weeks. The safety and efficacy of PULMICORT RESPULES when administered in excess of recommended doses have not been established. In all patients, it is desirable to downward-titrate to the lowest effective dose once asthma stability is achieved. The recommended starting dose and highest recommended dose of PULMICORT RESPULES, based on prior asthma therapy, are listed in the following table.

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Bronchodilators alone	0.5 mg total daily dose administered either once daily or twice daily in divided doses	0.5 mg total daily dose
Inhaled Corticosteroids	0.5 mg total daily dose administered either once daily or twice daily in divided doses	1 mg total daily dose
Oral Corticosteroids	1 mg total daily dose administered either as 0.5 mg twice daily or 1 mg once daily	1 mg total daily dose

In symptomatic children not responding to non-steroidal therapy, a starting dose of 0.25 mg once daily of PULMICORT RESPULES may also be considered.

If once-daily treatment with PULMICORT RESPULES does not provide adequate control of asthma symptoms, the total daily dose should be increased and/or administered as a divided dose.

Patients Not Receiving Systemic (Oral) Corticosteroids

Patients who require maintenance therapy of their asthma may benefit from treatment with PULMICORT RESPULES at the doses recommended above. Once the desired clinical effect is achieved, consideration should be given to tapering to the lowest effective dose. For the patients who do not respond adequately to the starting dose, consideration should be given to administering the total daily dose as a divided dose, if a once-daily dosing schedule was followed. If necessary, higher doses, up to the maximum recommended doses, may provide additional asthma control.

Patients Maintained on Chronic Oral Corticosteroids

Initially, PULMICORT RESPULES should be used concurrently with the patient's usual maintenance dose of systemic corticosteroid. After approximately one week, gradual withdrawal of the systemic corticosteroid may be initiated by reducing the daily or alternate daily dose. Further incremental reductions may be made after an interval of one or two weeks, depending on the response of the patient. Generally, these decrements should not exceed 25% of the prednisone dose or its equivalent. A slow rate of withdrawal is strongly recommended. During reduction of oral corticosteroids, patients should be carefully monitored for asthma instability, including objective measures of airway function, and for adrenal insufficiency (see WARNINGS). During withdrawal, some patients may experience symptoms of systemic corticosteroid withdrawal, eg, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement in pulmonary function. Such patients should be encouraged to continue with PULMICORT RESPULES but should be monitored for objective signs of adrenal insufficiency. If evidence of adrenal insufficiency occurs, the systemic corticosteroid doses should be increased temporarily and thereafter withdrawal should continue more slowly. During periods of stress or a severe asthma attack, transfer patients may require supplementary treatment with systemic corticosteroids.

A Pari-LC-Jet Plus Nebulizer (with face mask or mouthpiece) connected to a Pari Master compressor was used to deliver PULMICORT RESPULES to each patient in 3 U.S. controlled clinical studies. The safety and efficacy of PULMICORT RESPULES delivered by other nebulizers and compressors have not been established.

PULMICORT RESPULES should be administered via jet nebulizer connected to an air compressor with an adequate air flow, equipped with a mouthpiece or suitable face mask. Ultrasonic nebulizers are not suitable for the adequate administration of PULMICORT RESPULES and, therefore, are NOT recommended.

The effects of mixing PULMICORT RESPULES with other nebulizable medications have not been adequately assessed. PULMICORT RESPULES should be administered separately in the nebulizer (see PRECAUTIONS, Information for Patients).

Directions for Use

Illustrated *Patient's Instructions for Use* accompany each package of PULMICORT RESPULES.

HOW SUPPLIED

PULMICORT RESPULES is supplied in sealed aluminum foil envelopes containing one plastic strip of five single-dose RESPULES ampules together with patient instructions for use. There are 30 RESPULES ampules in a carton. Each single-dose RESPULES ampule contains 2 mL of sterile liquid suspension.

PULMICORT RESPULES is available in three strengths, each containing 2 mL:

NDC 0186-1988-04	0.25 mg/2 mL
NDC 0186-1989-04	0.5 mg/2 mL
NDC 0186-1990-04	1 mg/2 mL

Storage

PULMICORT RESPULES should be stored upright at controlled room temperature 20–25°C (68–77°F) [see USP], and protected from light. When an envelope has been opened, the shelf life of the unused RESPULES ampules is 2 weeks when protected. After opening the aluminum foil envelope, the unused RESPULES ampules should be returned to the aluminum foil envelope to protect them from light. Any opened RESPULES ampule must be used promptly. Gently shake the RESPULES ampule using a circular motion before use. Keep out of reach of children. Do not freeze.

Manufactured for: AstraZeneca LP, Wilmington, DE 19850
By: AstraZeneca AB, Södertälje, Sweden
Product of Sweden

30378-02 Rev. 06/07
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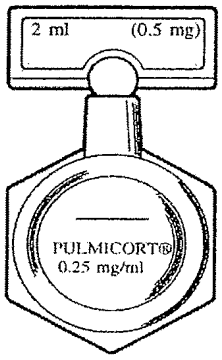
ASTRA
ASTRA DRACO

SPECIFICATION

Date		Specification No
94-02-23	PULMICORT suspension for nebulizing 0.25 mg/ml, single-dose units 2 ml	21-230-81/6
Product Company Astra Draco		Supersedes Specification No
Issued by		21-230-81/5 21-230-81/5B 21-230-81/5C
Prepared by		

	Description	An easily resuspendable white to off-white suspension filled into single-dose units made of LD-polyethylene. Manufactured in sheets of 5 units. Each unit is marked in black colour according to the figure. On the other side of the flat tab **BUDESONIDE** is embossed. The end pieces of each sheet are embossed with the batch number. Density: 1.002 kg/l



		Requirements
1	Appearance	An easily resuspendable white to off-white suspension filled into single-dose units made of plastic. Each unit is marked in black colour with **PULMICORT® 0.25 mg/ml** on the container body and with **2 ml** and **(0.5 mg)** on the flat tab (same side). On the other side of the flat tab **BUDESONIDE** is embossed. Sheets of 5 units. The end pieces of each sheet must be embossed with the batch number.
2	pH	4.0 - 5.0
3	Content	2.05 - 2.3 ml
4	Budesonide (identity)	Positive identity.
5	Budesonide	Release: 0.237 - 0.263 mg/ml Shelf life: 0.231 - 0.263 mg/ml
6	Particle measurement (Coulter Counter)	The particles will have a mass median diameter of 4 µm or less. At least 90 per cent (m/m) will be particles with a diameter of 7 µm or less.

Date 94-02-23 Product Company Astra Draco Issued by Prepared by EG	PULMICORT suspension for nebulizing 0.25 mg/ml, single-dose units 2 ml	Specification No 21-230-81/6 Supersedes Specification No 21-230-81/5 21-230-81/5B 21-230-81/5C

7	Degradation products	THIS TEST IS NOT PERFORMED AT THE RELEASE OCCASION. Not more than 2% in total related to the budesonide content. No individual peak exceeding 1 %.
8	Microbiological condition	Not more than 10^2 microorganisms per gram. No detectable pathogenic microorganisms. No increase in the number of microorganisms during storage.

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF PULMONARY DRUG PRODUCTS
HFD-570

5600 Fishers Lane, Rockville, MD 20857
Room 10B-45

PHONE: (301) 827-1050 FAX: (301) 827-1271

TO: Dennis Buccari

Phone: 508-836-8453

Fax: 508-836-8390

FROM: Gretchen

Total number of pages, including cover sheet: 7

Date: 12/12/96

REMARKS:

PRE-NDA CMC MEETING MINUTES

Date: November 20, 1996

Product: budesonide nebulizing suspension

IND: 44,535

Attendees

Astra USA:	Dennis Bucceri	Vice President Regulatory Affairs
	Murad Husain	Associate Director Regulatory Affairs
	Paul Alessandro	Regulatory Affairs
	Joseph Anisko	Quality Assurance
	Brian Graeff	Quality Assurance
	Larry Paglia	Quality Assurance
	Cheryl Larrivee-Elkins	Pharmaceutical Development
	William Hartnett	Operations
	Victor Keslake	Quality Assurance
Astra Draco:	Sedney Hugosson	Pharm./Analytical R&D
	Ann-Kristin Karlsson	Pharm./Analytical R&D
	Claes Ahlneck	Pharm./Analytical R&D
	Ove Molin	Quality Assurance (APL)
	Peter Akerman	Production (APL)
FDA:	John Jenkins	Director, Division of Pulmonary Drug Products
	Bob Meyer	Medical Team Leader
	Guirag Poochikian	Chemistry Team Leader
	Dale Koble	Chemistry Reviewer
	Linda Ng	Chemistry Reviewer
	Lindsay Cobbs	Project Manager
	Gretchen Trout	Project Manager

BACKGROUND: Astra requested a meeting with the Division of Pulmonary Drug Products to discuss their CMC program for budesonide nebulizing suspension (BNS). Astra intends to submit an NDA for this product in June of 1997. Astra submitted a meeting package dated October 30, 1996.

The meeting began with introductions, and Astra made a short presentation (see overheads attached). The following are clarifications that were made during the presentation.

- With regard to the primary packaging for BNS, the ampules are imprinted, not embossed.
- The budesonide content is an average of three units.

- The content uniformity was expressed around target fill because there is a 0.18 mL overfill volume per container.
- The fill volume is an average of 5 respules in a strip.
- When Astra upgrades to larger machines, it will not necessarily increase the filling time since the larger machines work faster. The time from filling to manufacture will stay the same.

After Astra's presentation, Dr. Koble informed Astra of the Division's issues with the drug substance. The following were Dr. Koble's comments.

- Some of the DMF's are deficient, and letters have already been issued to the DMF holders.
- Based on Pulmicort Turbuhaler, the particle size specification needs to be tightened, and the particle size by microscopy needs to have an upper limit for large particles. (Dr. Koble acknowledged that BNS is a different product from Pulmicort so the comments may not be exactly the same, but these are issues that Astra should keep in mind).
- Many specifications need to be tightened for related substances.
- There should be specifications for heavy metals, and the Division will consider a reduced program.
- The Division has concerns about the microbiological quality. The specification for the drug substance will have to be consistent with what is decided for the drug product.

Dr. Koble questioned Astra about the three stability studies on Diosynth substance, why was it not balanced between suppliers. Astra explained that there are 4 batches, 3 and 1 are matrixed from the 9 batches. For the lowest rank - 3 are on stability, 1 from Astra substance and the other 2 Diosynth substance. Dr. Poochikian questioned if it was feasible to introduce another batch of Astra chemical to be used in the drug product. If Astra has already started stability, the Division would have to look and see that they are comparable. Dr. Koble reminded Astra that with Rhinocort they ran into some stability problems. Dr. Koble questioned if all the contact surfaces in Sweden and the USA are the same. Astra replied that they are, and they will have 1 batch of each strength from Astra Sweden. Dr. Poochikian pointed out that since Astra is only using 1 batch of drug substance for everything, if there is a problem there will be no way to know if the problem is because of the drug substance or something else. Dr. Poochikian informed Astra that this was an issue for them to consider.

Dr. Ng then discussed issues relating to the drug product. Dr. Ng mentioned that the product is labeled sterile, however it is has not been sterilized. Astra replied that since it is a suspension, they have been unable to sterilize it by standard methods. Astra explained that if they sterilize the drug product by heat, it effects the particle size and

degradation, if they sterilize with ethylene oxide, residuals will remain, and if they sterilize by radiation, it effects the degradents. Dr. Poochikian stated that in general we expect inhalation products to be sterile, although we acknowledge that a suspension presents difficulties. Dr. Poochiklan suggested radiation techniques at lower levels with appropriate validation. Astra presented some overheads on the microbiological control of the drug product (see attached). Astra also stated that they attempted sterilizing the powder itself, and not the suspension, and that was not viable either. Dr. Koble questioned how there could be contamination, and yet there is no growth. Astra replied that they have done microbial challenge testing and it does not support growth, that this particular suspension is bactericidal in some instances and bacteriostasis in others. Dr. Poochiklan reemphasized that we expect the product to be sterilized, or alternatively Astra must provide data to show that it is bacteriostatic or bactericidal. Dr. Jenkins agreed, informing Astra that it is their burden to make the product sterile or justify why it can't be. Astra stated that they would put together a proposal and submit it to the Division for comment.

Dr. Ng made the following points with regard to the drug product.

- There are some concerns with the excipient polysorbate, however this will be discussed at the meeting with the toxicologists in December.
- With regard to specifications, Dr. Ng indicated that she could not comment at this time because Astra has not submitted any data. However, comments will be provided for the attributes tested.
- With regard to attributes, for particle size the Division prefers to see a distribution profile rather than a single time point.
- For droplet size, the Division wants to know the distribution of the spray droplets from the nebulizer under *in vitro* conditions.
  For osmolarity, there should be a test for release.
- For the container, appropriate DMF references should be made.
- Dr. Ng questioned if Astra will test for water loss from the closed container. Astra agreed that they could do that.
- Express assay on per container basis is recommended (see discussion on overfill).
- Photostability studies should be submitted as per ICH.
- Data should be submitted to support stability - physical, chemical and microbiological, for the 10 day manufacutring fill time.
- Astra should test for leachables into the container; e.g., ink, etc.

Dr. Ng questioned Astra about one of their overheads where they mentioned "dispensed dose (resuspendability)". Astra explained that they open the container, squeeze out the dose and analyze with liquid chromatography. They get the dose in mL and then normalize to 2mL. Astra does this to see whether there is suspendability,

it is a physical test not an actual dose.

Dr. Ng informed Astra that for their stability studies, since this product is aqueous based, high humidity might not be relevant, however Astra should refer to the ICH guidelines. Dr. Poochikian added that the ICH guidelines do not discuss long-term data, only accelerated data, however the Agency recommends not more then 40% humidity. Astra questioned if the Division would want to see these data even on the foiled units. Dr. Poochikian replied that the data is definitely needed for the unfoiled units, for the foiled units the Division will discuss internally and get back to Astra with an answer.

Dr. Ng informed Astra that for the storage temperature Astra should look at 30° in addition to the 25° and 40° that they proposed. Dr. Poochikian explained that the Division requests 30° in case there is a problem at 40°. If everything is acceptable at 40°, then Astra will not need to generate data at 30°.

In addition to the Division's comments, Astra requested feedback from the Division on Astra's overfill of containers. Astra overfills the containers by 0.18 mL in order to assuredly deliver 2.0 mL (see overhead). The variation in nebule content is 2.05-2.30 mL. Dr. Poochikian informed Astra that the Division would discuss this internally and get back to Astra with a response. Dr. Poochikian informed Astra that based on the overfill, how Astra expresses content uniformity might be effected. The Division prefers to express content uniformity as the percent of labeled claim. Astra presented an overhead illustrating distribution, and verified that this overfill was also true of the clinical batches.

Dr. Poochikian encouraged Astra to develop a method, and set specifications for, foreign particulate in addition to their drug substance particles. The foreign particulates could come from the tubing, closure system, etc.

With regard to the Romelac 3012 and the 4010, the difference between the two machines is the capacity. However the machines use the same temperature, molds, contact surfaces, etc. Astra was told that they need to describe in the NDA the similarities and/or differences between the two machines.

In addition, the following points were clarified by Astra.

- Astra will conduct a study where they remove the respules from the foil package, put into paper envelopes and store in a controlled dark room. The purpose of the study is to simulate patient use. The instructions tell consumers to use the respules within 3 months after removing from the foil, and to keep them in a dark place.

- There will be a lot number and expiration date printed on each respule unit on the tab.

With regard to labeling, the Division informed Astra that for these types of preparations, the drug should be expressed as an amount, instead of concentration. Dr. Jenkins questioned if Astra included instructions to shake the respule prior to using due to the settling of the suspension. Astra replied that there were such instructions. Dr. Jenkins questioned also if Astra had conducted any *in vitro* testing with the nebulizer when the product hadn't been shaken or swirled, to determine if it effects the amount of drug delivered. The directions will have to be specific because if the respule is shaken too hard it foams, and if it is not shaken the suspension stays in the container. Dr. Poochikian stated that it might be appropriate for Astra to see how much residual drug is left behind after nebulization. Astra replied that they have data on that and will include it in the NDA.

Astra was reminded to be aware in their studies for solvent migration, of the ink and the solvent.

With regard to microbiology, in the NDA Astra was told to justify the 10 day storage time. Astra needs to document and supply validation data.

Gretchen Trout
Project Manager

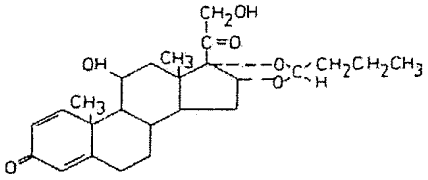
(2)

Exhibit 9

ASTRA | Astra Pharmaceutical Production AB

SPECIFICATION

Date (Yr. Mo. Day)	Product	Specification No.	Page
83 11 18	Budesonide micronized sterile	22-134-11/2	1/2
Issued by: DRACO NG	(Budesonid mikroniserad steril)	Product Code No.: 22-134-11	
Prepared by: NG		Supersedes Specification No.: H-B-29-1	

	Synonyms	16α,17α-Butylidenedioxypregna-1,4-diene-11β,21 - diol - 3,20 - dione. S-1320 (laboratory code).
	Structural formula	
	Molecular formula	$C_{25}H_{34}O_6$
	Molecular weight	430.5
	Description	Budesonide is a mixture of two epimeric forms, epimer A and epimer B. A white to off-white fine powder, freely soluble in chloroform, sparingly soluble in ethanol, practically insoluble in water and in heptane. It melts at 224°C to 231.5°C with decomposition (Epimer A:B, 50:50).
	Storage	In well-closed, sterile containers, protected from light.
		Requirements
1	Appearance	A white to off-white, fine powder.
2	IR-spectrum	Conforms to a reference spectrum.
3	Loss on drying	Not more than 0.8 per cent.
4	Particle size	50 per cent (w/w) will be particles with a mass-equivalent sphere of 4 µm or less. At least 85 per cent (w/w) will be particles with a mass-equivalent sphere of 7 µm or less.
5	Foreign steroids	Not more than 2 per cent determined by HPLC; no individual foreign steroid exceeding 0.5 per cen
6	Epimer A	40 - 51 per cent, determined by HPLC and related to the content of budesonide.

Astra Pharmaceutical Production AB

SPECIFICATION

(Year, Mo, Day)	Product	Specification No.	Page
93 11 18	Budesonide micronized sterile	22-134-11/2	2/2
Issued by: DRACO NG	(Budesonid mikroniserad steril)	Product Code No.: 22-134-11	
Prepared by: NG		Supersedes Specification No.: H-B-29-1	

7	Budesonide	98 - 102 per cent, calculated with reference to the dried substance; determined by HPLC.
8	Sterility	Sterile according to Ph.Eur.

ASTRA

TILLVERKNINGSMETOD

Produktnamn	PREFERID kräm 0,025% (f. Norden)
Beredningsform/produkttyp	kräm
Kod nr	20-091-24
Metoden tillämpas f o m batch nr	14
Föregående metod daterad	1979 03 20
Utfärdad av, bolag	DRACO
avdelning	Galeniska laboratoriet
namn	Lennart Wenngren
datum	1980 09 09

Princip för tillverkningen

Krämen skall beredas och fyllas aseptiskt. Den sterila steroiden suspenderas i sterilt vatten. Resterande råvaror smältes och autoklaveras i salvblandaren. Faserna homogeniseras vid 70°C och krämen kyles till 30°C. Därefter tillsättes steroid-vatten-suspensionen och krämen homogeniseras åter. Undertryck och kvävgas användes under blandning och homogenisering.

Hygienstandard

Krämen beredes och fylles i lokaler av renhetsklass III avsedda för aseptisk beredning och hantering. All produktberörande utrustning och apparatur skall vara steril och torr.

Apparatur

Steriliserbar salvblandare och homogenisator.
Kärl av glas eller rostfritt stål.
Grovfilter (t.ex. Pall MCY 1001 filter).

Sammansättning och råvaror till 500 kg

22-134-11	Budesonid mikro steril	0,125 kg x)
39-300-13	Paraffin flytande	5,000 kg
39-371-17	Vaselin, vit	25,000 kg
39-699-12	Cetostearylalkohol	50,000 kg
39-695-16	Cetomacrogol 1000	10,000 kg
35-166-14	Sorbinsyra	0,500 kg
35-029-29	Citronsyra	0,500 kg
35-120-19	Natriumcitrat	1,000 kg
29-092-32	Vatten, destillerat	408,000 kg
		500,125 kg

Budesonid mikro steril är etylenoxid steriliserad och satsas efter halt 128,8 - 125,0 (97-100%).

Beredning av 500 kg kräm

1. Vaselin 25,000 kg
Cetostearylalkohol 50,000 kg
Paraffin flytande 5,000 kg
Cetomacrogol 1000 9,995 kg

Den feta fasen smältes och pumpas via ett grovfilter till salvblandaren.

2. Citronsyra 0,500 kg
Natriumcitrat 1,000 kg
Sorbinsyra 0,500 kg
Vatten, destillerat 383,000 kg

När substanserna har löst sig, klarfiltreras lösningen direkt ner i salvblandaren.

3. Blandaren evakueras −(60-80) kPa, därefter genombubblas innehållet (1+2) i blandarkärlet med N_2-gas i 15 min. De båda faserna 1 och 2 autoklaveras vid 120°C under 20 min, därefter kyles krämblandningen till 70°C och evakueras −(60-80) kPa. När innehållet är luftfritt homogeniseras de båda faserna med högsta hastighet på homogenisatorer och rörverktyg i 15 min. Blandningen evakueras ånyo −(60-80) kPa, samt kyles till 30°C ± 2 under omrörning.

4. Dispergering av budesonid mikro steril:

I två lämpliga kärl autoklaveras

Vatten renat	25,0	kg
Cetomacrogol 1000	0,005	kg

I det ena kärlet autoklaveras ca 6-8 kg vatten, renat och Cetomacrogol.
I det andra kärlet autoklaveras ca 17-19 kg vatten renat.

I ett lämpligt autoklaverat kärl överföres

Budesonid mikro steril	0,125 kg	(100%-ig)

till ca 4-5 kg av den autoklaverade Cetomacrogol-lösningen. Suspensionen köres i Ultra Turrax i minst 10 min. Resterande mängd Cetomacrogol-lösning användes till att skölja burken samt kärlet vid överföringen till ett större kärl, vilket innehåller autoklaverat vatten. Suspensionen köres ånyo i Ultra Turrax i minst 10 min. Suspensionen satsas till salvblandaren. Kärlet sköljes med en mindre mängd vatten som satsas till blandaren.

5. Innan rörverktyg och homogenisator startas, skall blandaren evakueras (60-80) kPa. Under vakuum blandas steroid-suspensionen med krämen i salvblandaren med högsta hastighet på omrörare och homogenisator under 15 minuter.
Kärlet tryckutjämnas med N_2-gas.

6. Den färdiga krämen fylles på sterila kärl i avvaktan på fyllning.

ASTRA

MANUFACTURING METHOD

Name of product	PREFERID cream 0.025% (from Norden)
Preparation form/product type	cream
Code no.	20-091-24
This method is valid from batch no.	14
Date of previous method	20 3 1979
Issued by, company	DRACO
department	Galenic laboratory
name	*(signature)* Lennart Wenngren
date	9 9 1980

Outline of manufacturing
The cream is prepared and filled aseptically. The sterile steroid is suspended in sterile water. The remaining raw materials are melted and autoclaved in the mixer. The phases are homogenised at 70°C and the cream is cooled to 30°C. The steroid and water suspension is then added and the cream is homogenised again. Negative pressure and nitrogen gas are used during mixing and homogenisation.

Hygiene standard
The cream is prepared and filled in class III clean rooms designated for aseptic preparation and handling. All equipment and apparatus that touches the product must be sterile and dry.

Apparatus
Sterilisable mixer and homogeniser.
Vessels made of glass or stainless steel.
Coarse filter (e.g. Pall filter, MCY 1001).

Manufacture of 500 kg of cream

1. | | |
|---|---|
| Vaseline | 25.000 kg |
| Cetostearyl alcohol | 50.000 kg |
| Liquid paraffin | 5.000 kg |
| Cetomacrogol 1000 | 9.995 kg |

The fatty phases are melted and pumped through a coarse filter into the mixer.

2. | | |
|---|---|
| Citric acid | 0.500 kg |
| Sodium citrate | 1.000 kg |
| Sorbic acid | 0.500 kg |
| Distilled water | 383.000 kg |

When the ingredients have dissolved the solution is clear filtered directly down into the mixer.

3. The mixer is evacuated -(60-80) kPa, and then N_2 gas is bubbled through the contents (1+2) in the mixing vessel for 15 minutes. The two phases 1 and 2 are autoclaved at 120°C for 20 minutes, after which the cream mixture is cooled to 70°C and evacuated -(60-80) kPa. When the contents are deaerated the two phases are homogenised at the highest possible speed in the homogeniser and stirrer for 15 minutes. The mixture is evacuated again -(60-80) kPa and cooled to 30°C ± 2 while being stirred.

4. Dispersion of budesonide micronised, sterile:

Purified water	25.0 kg
Cetomacrogol 1000	0.005 kg

are autoclaved in two suitable vessels.
About 6-8 kg purified water and cetomacrogol are autoclaved in one vessel.
About 17-19 kg purified water is autoclaved in the other vessel.

Budesonide micronised, sterile 0.125 kg (100%)
is transferred into a suitable, autoclaved vessel into about 4-5 kg of the autoclaved cetomacrogol solution. The suspension is agitated in the Ultra Turrax for at least 10 minutes. The remaining quantity of cetomacrogol solution is used to rinse the jar and the vessel for transfer into a large vessel that contains autoclaved water. The suspension is agitated again in the Ultra Turrax for at least 10 minutes. The suspension is added to the mixer. The vessel is rinsed with a small quantity of water, which is added to the mixer.

5. Before the stirrer and homogeniser are started, the mixer must be evacuated [redacted](60-80) kPa. Under vacuum the steroid suspension is mixed with the cream in the mixer at the highest possible speed in the homogeniser and stirrer for 15 minutes.
The vessel pressure is equalised with N_2 gas.

6. The finished cream is filled into sterile vessels to await filling.

GUIDE TO INSPECTIONS OF STERILE DRUG SUBSTANCE MANUFACTURERS

Note: This document is reference material for investigators and other FDA personnel. The document does not bind FDA, and does no confer any rights, privileges, benefits, or immunities for or on any person(s).

One of the more difficult processes to inspect and one which has presented considerable problems over the years is that of the manufacture of sterile bulk drug substances. Within the past several years, there have been a number of batches of sterile bulk drug substances from different manufacturers which exhibited microbiological contamination. One manufacturer had approximately 100 batches contaminated in a 6 month time period. Another had approximately 25 batches contaminated in a similar period. Other manufacturers have had recalls due to the lack of assurance of sterility. Although the Inspection Guide for Bulk Drug Substances provides some direction for the inspection of the sterile bulk drug substance, it does not provide the detailed direction needed.

I. INTRODUCTION

In the manufacture of the sterile bulk powders, it is important to recognize that there is no further processing of the finished sterile bulk powder to remove contaminants or impurities such as particulates, endotoxins and degradants.

As with other inspections, any rejected batches, along with the various reasons for rejection, should be identified early in the inspection to provide direction for the investigator. For example, lists of batches rejected and/or retested over a period of time should be obtained from the manufacturer to provide direction for coverage to be given to specific processes or systems. Because some of the actual sterile bulk operations may not be seen, and because of the complexity of the process, it is particularly important to review reports and summaries, such as validation studies, reject lists, Environmental Monitoring Summary Reports, QA Investigation Logs, etc. These systems and others are discussed in the Basic Inspection Guide. This is particularly important for the foreign sterile bulk drug substance manufacturer where time is limited.

In the preparation for a sterile bulk drug substance inspection, a flow chart with the major processing steps should be obtained. Generally, the manufacture of a sterile bulk substance usually includes the following steps:

1. Conversion of the non-sterile drug substance to the sterile form by dissolving in a solvent, sterilization of the solution by filtration and collection in a sterilized reactor (crystallizer).

2. Aseptic precipitation or crystallization of the sterile drug substance in the sterile reactor.

3. Aseptic isolation of the sterile substance by centrifugation or filtration.

4. Aseptic drying, milling and blending of the sterile substance.

5. Aseptic sampling and packaging the drug substance.

These operations should be performed in closed systems, with minimal operator handling. Any aseptic operations performed by an operator(s) other than in a closed system should be identified and carefully reviewed.

II. COMPONENTS

In addition to the impurity concerns for the manufacture of bulk drug substances, there is a concern with endotoxins in the manufacture of the sterile bulk drug substances. The validation report, which demonstrates the removal, if present, of endotoxins to acceptable levels, should be reviewed. Some

manufacturers have commented that since an organic solvent is typically used for the conversion of the non-sterile bulk drug substance to the sterile bulk drug substance, that endotoxins will be reduced at this stage. As with any operation, this may or may not be correct. For example, in an inspection of a manufacturer who conducted extensive studies of the conversion (crystallization) of the non-sterile substance to the sterile drug substance, they found no change from the initial endotoxin level. Organic solvents were used in this conversion. Thus, it is important to review and assess this aspect of the validation report.

In the validation of this conversion (non-sterile to sterile) from an endotoxin perspective, challenge studies can be carried out on a laboratory or pilot scale to determine the efficiency of the step. Once it is established that the process will result in acceptable endotoxin levels, some monitoring of the production batches would be appropriate. As with any validation process, the purpose and efficiency of each step should be evaluated. For example, if the conversion (crystallization) from the non-sterile to the sterile substance is to reduce endotoxins by one log, then data should support this step.

Since endotoxins may not be uniformly distributed, it is also important to monitor the bioburden of the non-sterile substance(s) being sterilized. For example, gram negative contaminats in a non-sterile bulk drug substance prior to sterilization are of concern, particularly if the sterilization (filtration) and crystallization steps do not reduce the endotoxins to acceptable levels. Therefore, microbiological, as well as endotoxin data on the critical components and operational steps should be reviewed.

III. FACILITY

Facility design for the aseptic processing of sterile bulk drug substances should have the same design features as an SVP aseptic processing facility. These would include temperature, humidity and pressure control. Because sterile bulk aseptic facilities are usually larger, problems with pressure differentials and sanitization have been encountered. For example, a manufacturer was found to have the gowning area under greater pressure than the adjacent aseptic areas. The need to remove solvent vapors may also impact on area pressurization.

Unnecessary equipment and/or equipment that cannot be adequately sanitized, such as wooden skids and forklift trucks, should be identified. Inquire about the movement of large quantities of sterile drug substance and the location of pass-through areas between the sterile core and non-sterile areas. Observe these areas, review environmental monitoring results and sanitization procedures.

The CGMP Regulations prohibit the use of asbestos filters in the final filtration of solutions. At present, it would be difficult for a manufacturer to justify the use of asbestos filters for filtration of air or solutions. Inquire about the use of asbestos filters.

Facilities used for the charge or addition of non-sterile components, such as the non-sterile drug substance, should be similar to those used for the compounding of parenteral solutions prior to sterilization. The concern is soluble extraneous contaminants, including endotoxins, that may be carried through the process. Observe this area and review the environmental controls and specifications to determine the viable and non-viable particulate levels allowed in this area.

IV. PROCESSING

Sterile powders are usually produced by dissolving the non-sterile substance or reactants in an organic solvent and then filtering the solution through a sterilizing filter. After filtration, the sterile bulk material is separated from the solvent by crystallization or precipitation. Other methods include dissolution in an aqueous solution, filtration sterilization and separation by crystallization/filtration. Aqueous solutions can also be sterile filtered and spray dried or lyophilized.

In the handling of aqueous solutions, prior to solvent evaporation (either by spray drying or

lyophilization), check the adequacy of the system and controls to minimize endotoxin contamination. In some instances, piping systems for aqueous solutions have been shown to be the source of endotoxin contamination in sterile powders. There should be a print available of the piping system. Trace the actual piping, compare it with the print and assure that there are no "dead legs" in the system.

The validation data for the filtration (sterilization) process should also be reviewed. Determine the firm's criteria for selection of the filter and the frequency of changing filters. Determine if the firm knows the bioburden and examine their procedures for integrity testing filters.

Filters might not be changed after each batch is sterilized. Determine if there is data to justify the integrity of the filters for the time periods utilized and that "grow through" has not occurred.

In the spray drying of sterile powders, there are some concerns. These include the sterilization of the spray dryer, the source of air and its quality, the chamber temperatures and the particle residence or contact time. In some cases, charring and product degradation have been found for small portions of a batch.

With regard to bulk lyophilization, concerns include air classification and aseptic barriers for loading and unloading the unit, partial meltback, uneven freezing and heat transfer throughout the powder bed, and the additional aseptic manipulations required to break up the large cake. For bulk lyophilization, unlike other sterile bulk operations, media challenges can be performed. At this point in time, with today's level of technology, it would seem that it would be difficult to justify the bulk lyophilization of sterile powders (from a microbiological aspect). Refer to the Guide for the Inspection of a Lyophilization Process for additional direction regarding this process.

Seek to determine the number and frequency of process changes made to a specific process or step. This can be an indicator of a problem experienced in a number of batches. A number of changes in a short period of time can be an indicator that the firm is experiencing problems. Review the Process Change SOP and the log for process changes, including the reason for such changes.

V. EQUIPMENT

Equipment used in the processing of sterile bulk drug substances should be sterile and capable of being sterilized. This includes the crystallizer, centrifuge and dryer. The sanitization, rather than sterilization of this equipment, is unacceptable. Sterilization procedures and the validation of the sterilization of suspect pieces of equipment and transfer lines should be reviewed.

The method of choice for the sterilization of equipment and transfer lines is saturated clean steam under pressure. In the validation of the sterilization of equipment and of transfer systems, Biological Indicators (BIs), as well as temperature sensors (Thermocouple (TC) or Resistance Thermal Device (RTD)) should be strategically located in cold spots where condensate may accumulate. These include the point of steam injection and steam discharge, as well as cold spots, which are usually low spots. For example, in a recent inspection, a manufacturer utilized a Sterilize-In-Place (SIP) system and only monitored the temperature at the point of discharge and not in low spots in the system where condensate can accumulate.

The use of formaldehyde is a much less desirable method of sterilization of equipment. It is not used in the United States, primarily because of residue levels in both the environment and in the product. A major problem with formaldehyde is its removal from piping and surfaces. In the inspection of a facility utilizing formaldehyde as a sterilant, pay particular attention to the validation of the cleaning process. The indirect testing of product or drug substance to demonstrate the absence of formaldehyde levels in a system is unacceptable. As discussed in the Cleaning Validation Guide, there should be some direct measure or determination of the absence of formaldehyde. Since contamination in a system and in a

substance is not going to be uniform, merely testing the substance as a means of validating the absence of formaldehyde is unacceptable. Key surfaces should be sampled directly for residual formaldehyde.

One large foreign drug substance manufacturer, after formaldehyde sterilization of the system, had to reject the initial batches coming through the system because of formaldehyde contamination. Unfortunately, they relied on end product testing of the product and not on direct sampling to determine the absence of formaldehyde residues on equipment.

SIP systems for the bulk drug substance industry require considerable maintenance, and their malfunction has directly led to considerable product contamination and recall. The corrosive nature of the sterilant, whether it is clean steam, formaldehyde, peroxide or ethylene oxide, has caused problems with gaskets and seals. In two cases, inadequate operating procedures have led to even weld failure. For example, tower or pond water was inadvertently allowed to remain in a jacket and was valved shut. Clean steam applied to the tank resulted in pressure as high as 1,000 lbs., causing pinhole formation and contamination. Review the equipment maintenance logs. Review non-schedule equipment maintenance and the possible impact on product quality. Identify those suspect batches manufactured and released prior to the repair of the equipment.

Another potential problem with SIP systems is condensate removal from the environment. Condensate and excessive moisture can result in increased humidity and increases in levels of microorganisms on surfaces of equipment. Therefore, it is particularly important to review environmental monitoring after sterilization of the system.

The sterile bulk industry, as the non-sterile bulk industry, typically manufactures batches on a campaign basis. While this may be efficient with regard to system sterilization, it can present problems when a batch is found contaminated in the middle of a campaign. Frequently, all batches processed in a campaign in which a contaminated batch is identified are suspect. Review the failure investigation reports and the logic for the release of any batches in a campaign. Some of the more significant recalls have occurred because of the failure of a manufacturer to conclusively identify and isolate the source of a contaminant.

VI. ENVIRONMENTAL

MONITORING

The environmental monitoring program for the sterile bulk drug substance manufacturer should be similar to the programs employed by the SVP industry. This includes the daily use of surface plates and the monitoring of personnel. As with the SVP industry, alert or action limits should be established and appropriate follow-up action taken when they are reached.

There are some bulk drug substance manufacturers that utilize UV lights in operating areas. Such lights are of limited value. They may mask a contaminant on a settling or aerobic plate. They may even contribute to the generation of a resistant (flora) organism. Thus, the use of Rodac or surface plates will provide more information on levels of contamination.

There are some manufacturers that set alert/action levels on averages of plates. For the sampling of critical surfaces, such as operators' gloves, the average of results on plates is unacceptable. The primary concern is any incidence of objectionable levels of contamination that may result in a non-sterile product.

As previously discussed, it is not unusual to see the highest level of contamination on the surfaces of equipment shortly after systems are steamed. If this occurs, the cause is usually the inadequate removal of condensate.

Since processing of the sterile bulk drug substance usually occurs around the clock, monitoring surfaces

and personnel during the second and third shifts should be routine.

In the management of a sterile bulk operation, periodic (weekly/monthly/quarterly) summary reports of environmental monitoring are generated. Review these reports to obtain those situations in which alert/action limits were exceeded. Review the firm's investigation report and the disposition of batches processed when objectionable environmental conditions existed.

VII. VALIDATION

The validation of the sterilization of some of the equipment and delivery systems and the validation of the process from an endotoxin perspective have been discussed.

In addition to these parameters, demonstration of the adequacy of the process to control other physicochemical aspects should also be addressed in a validation report. Depending upon the particular substance, these include potency, impurities, particulate matter, particle size, solvent residues, moisture content, and blend uniformity. For example, if the bulk substance is a blend of two active substances or an active substance and excipient, then there should be some discussion/evaluation of the process for assuring uniformity. The process validation report for such a blend would include documentation for the evaluation and assurance of uniformity. A list of validation reports and process variables evaluated should be reviewed.

As with a non-sterile bulk drug substance, there should be an impurity profile and specific, validated analytical methods. Those should also be reviewed.

Manufacturers are expected to validate the aseptic processing of sterile BPCs. Such validation must encompass all parts, phases, steps, and activities of any process where components, fluid pathways, in-process fluids, etc., are expected to remain sterile. Furthermore, such validation must include all probable potentials for loss of sterility as a result of processing. Validation must also account for all potential avenues of microbial ingress associated with the routine use of the process.

The validation procedure should approximate as closely as possible all those processing steps, activities, conditions, and characteristics that may have a bearing on the possibility of microbial ingress into the system during routine production. In this regard, it is essential that validation runs are as representative aspossible of routine production to ensure that the results obtained from validation are generalizable to routine production.

Validation must include the 100% assessment of sterility of an appropriate material that is subjected to the validation procedure. Culture media is the material of choice. whenever feasible. Where not feasible, non-media alternatives would be acceptable. Where necessary, different materials can be used in series for different phases of a composite aseptic process incapable of accommodating a single material. In any event, some material simulating the sterile BPC, or the sterile BPC itself, must pass through the entire system that is intended to be sterile. Any material used for process validation must be microbiologically inert.

Environmental and personnel monitoring must be performed during validation, in a manner and amount sufficient to establish appropriate monitoring limits for routine production.

At least three consecutive, successful validation runs are necessary before an aseptic process can be considered to be validated.

Alternative proposals for the validation of the aseptic processing of bulk pharmaceuticals will be considered by FDA on a case-by-case basis. For example, it may be acceptable to exclude from the aseptic processing validation procedure certain stages of the post-sterilization bulk process that take place in a totally closed system. Such closed systems should be sterilized in place by a validated

procedure, integrity tested for each lot, and should not be subject to any intrusions whereby there may be the likelihood of microbial ingress. Suitable continuous system pressurization would be considered an appropriate means for ensuring system integrity.

VIII. WATER FOR INJECTION

Although water may not be a component of the sterile drug substance, water that comes in contact with the equipment or that enters into the reaction can be a source of impurities (e.g., endotoxins). Therefore, only water for injection should be utilized.

Some manufacturers have attempted to utilize marginal systems, such as single pass Reverse Osmosis (RO) systems. For example, a foreign drug substance manufacturer was using a single pass RO system with post RO sterilizing filters to minimize microbiological contamination. This system was found to be unacceptable. RO filters are not absolute and should therefore be in series. Also, the use of sterilizing filters in a Water for Injection system to mask a microbiological (endotoxin) problem has also been unacceptable. As with environmental monitoring, periodic reports should be reviewed.

If any questionable conditions are found, refer to the Inspection Guide for High Purity Water Systems.

IX. TERMINAL STERILIZATION

There are some manufacturers who sterilize bulk powders after processing, by the use of ethylene oxide or dry heat. Some sterile bulk powders can withstand the lengthy times and high temperatures necessary for dry heat sterilization. In the process validation for a dry heat cycle for a sterile powder, important aspects that should be reviewed include: heat penetration and heat distribution, times, temperatures, stability (in relation to the amount of heat received), and particulates.

With regard to ethylene oxide, a substantial part of the sterile bulk drug industry has discontinued the use of ethylene oxide as a "sterilizing" agent. Because of employee safety considerations, ethylene oxide residues in product and the inability to validate ethylene oxide sterilization, its use is on the decline. As a primary means of sterilization, its utilization is questionable because of lack of assurance of penetration into the crystal core of a sterile powder.

Ethylene oxide has also been utilized in the treatment of sterile powders. Its principal use has been for surface sterilization of powders as a precaution against potential microbiological contamination of the sterile powder during aseptic handling.

There are some manufacturers of ophthalmics that continue to use it as a sterilant for the drug used in the formulation of sterile ophthalmic ointments and suspensions. If used as a primary sterilant, validation data should be reviewed. Refer to the Inspection Guide for Topical Products for further discussion.

X. REWORK/REPROCESSING/

RECLAMATION

As with the principal manufacturing process, reprocessing procedures should also be validated. Additionally, these procedures must be approved in filings.

Review reprocessed batches and data that were used to validate the process. Detailed investigation reports, including the description, cause, and corrective action should be available for the batch to be reprocessed.

XI. LABORATORY TESTING

AND SPECIFICATIONS

The sterility testing of sterile bulk substances should be observed. Additionally, any examples of initial

sterility test failures should be investigated. The release of a batch, particularly of a sterile bulk drug substance, which fails an initial sterility test and passes a retest is very difficult to justify. Refer to the Microbiological Guide and Laboratory Guide for additional direction.

Particulate matter is another major concern with sterile powders. Specifications for particulate matter should be tighter than the compendial limits established for sterile dosage forms. The subsequent handling, transfer and filling of sterile powders increases the level of particulates. It is also important to identify particulates so that their source can be determined. Review the firm's program for performing particulate matter testing. If there are no official limits established, review their release criteria for particulates, and the basis of their limit.

With regard to residues, since some sterile powders are crystallized out of organic solvents, low levels of these solvents may be unavoidable. In addition to evaluation of the process to assure that minimal levels are established, data used by the firm to establish a residue level should be reviewed. Obviously, each batch should be tested for conformance with the residue specification. Refer to the Inspection Guide for Bulk Drug Substances for additional direction regarding limits for impurities.

XII. PACKAGING

Sterile bulk drug substances are filled into different type containers which include sterile plastic bags and sterile cans. With regard to sterile bags, sterilization by irradiation is the method of choice because of the absence of residues. There are some manufacturers, particularly foreign, which utilize formaldehyde. A major disadvantage is that formaldehyde residues may and frequently do appear in the sterile drug substance. Consequently, we have reservations about the acceptability of the use of formaldehyde for, container sterilization because of the possibility of product contamination with formaldehyde residues.

If multiple sterile bags are used, operations should be performed in aseptic processing areas. Since the dosage form manufacturer expects all inner bags to be sterile, outer bags should be applied over the primary bag containing the sterile drug in an aseptic processing area. One large manufacturer of a sterile powder only applied the immediate or primary bag in an aseptic processing area. Thus, the outer portion of this primary bag was contaminated when the other bags were applied over this bag in non-sterile processing areas.

With regard to sterile cans, a concern is particulates, which can be generated due to banging and movement. Because of some with trace quantities of aluminum, companies have moved to stainless steel cans.

The firm's validation data for the packaging system should be reviewed. Important aspects of the sterile bag system include residues, pinholes, foreign matter (particulates), sterility and endotoxins. Important aspects of the rigid container systems include moisture, particulates and sterility.

Page Updated: July 13, 2005

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- Biotechnology
- Biologics
- Computer Issues
- Devices
- Drugs
- Foods Cosmetics
- Miscellaneous

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- INFECTIOUS DISEASE MARKER TESTING FACILITIES (6/96)
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- GLOSSARY COMP. SYSTEMS. SOFTWARE DEVELOPMENT TERMINOLOGY(8/95)

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- ELECTROMAGNECTIC COMPATIBILITY ASPECTS OF MEDICAL DEVICE QUALITY SYSTEMS
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- MEDICAL DEVICE MANUFACTURERS

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- LYOPHILIZATION OF PARENTERALS(7/93)
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- PHARMACEUTICAL QUALITY CONTROL LABORATORIES (7/93)
- VALIDATION OF CLEANING PROCESSES(7/93)
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- ORAL SOLID DOSAGE FORMS PRE/POST APPR. ISSUES (1/94)
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- TOPICAL DRUG PRODUCTS(7/94)
- ORAL SOLUTIONS AND SUSPENSIONS(8/94)

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- NUTRITIONAL LABELING AND EDUCATION ACT (NLEA) REQUIREMENTS (8/94-2/95)
- COSMETIC PRODUCT MANUFACTURERS(2/95)
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- LOW ACID CANNED FOOD MANUFACTURERS Part 2 - PROCESSES/PROCEDURES
- LOW ACID CANNED FOOD MANUFACTURERS Part 3 - CONTAINERS/CLOSURES (11/98)
- ACIDIFIED FOOD MANUFACTURERS
- TRACEBACK OF FRESH FRUITS AND VEGETABLES IMPLICATED IN EPIDEMIOLOGICAL INVESTIGATIONS

- SALMONELLA ENTERITIDIS (SE) GUIDE TO TRACEBACK IN EGGS (07/03/2003)

MISCELLANEOUS

- FOREIGN MEDICAL DEVICE MANUFACTURERS(9/95)
- FOREIGN PHARMACEUTICAL MANUFACTURERS(5/96)

Exhibit R

APPLIED MICROBIOLOGY, Aug. 1968, p. 1110–1113

Vol. 16, No. 8
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Dry Heat or Gaseous Chemical Resistance of *Bacillus subtilis* var. *niger* Spores Included Within Water-soluble Crystals

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Received for publication 13 May 1968

Inclusion of spores of *Bacillus subtilis* var. *niger* in water-soluble crystals increased the resistance of the spores to dry heat and to a gaseous mixture of methyl bromide and ethylene oxide. Resistance of spores in glycine crystals to dry heat at 125 C was increased 5 to 24 times compared to unprotected spores. There appeared to be a positive correlation between the size of the crystal and the degree of resistance. The resistance to dry heat of spores included in sodium chloride crystals was about six times greater than unprotected spores. A gaseous mixture of methyl bromide (964 mg/liter) and ethylene oxide (642 mg/liter) at 37% relative humidity was ineffective in sterilizing spores enclosed within these water-soluble crystals, as was ethylene oxide alone. However, if the relative humidity was sufficiently high to dissolve the crystals during exposure to the vapor, viable-spore counts were drastically reduced or were negative. The surfaces of crystals grossly contaminated with dry spores were sterilized by exposure to gaseous ethylene oxide. Sterilization of heat-labile or moisture-labile materials with a critical requirement for sterility, as in planetary probes or drugs, may be complicated by the presence of spores in naturally occurring water-soluble crystals. This phenomenon is similar to the protection afforded spores entrapped in solid plastics.

Widespread use of ethylene oxide (ETO) has filled an urgent need for a means of sterilizing heat-labile and moisture-labile materials. However, ETO and other sterilizing gases are effective only if they can contact the microorganisms. Numerous substances can provide an impermeable barrier to these gases. Several investigators have observed the resistance of spores trapped in crystals to sterilization by gaseous chemicals. Kaye and Phillips (5) observed that spores suspended in NaCl solutions and dried under vacuum on metal or glass for 5 hr were more resistant to sterilization with gaseous ETO than spores dried from distilled water and subjected to the same treatment. Abbott, Cockton, and Jones (1) reported that spores included in Rochelle salt crystals resisted sterilization with formaldehyde and ETO. They also found that spores in glycine crystals were not sterilized when exposed to formaldehyde. Royce and Bowler (9) noted that bacteria in crystals of glucose, NaCl, and other pharmaceutical products were protected against sterilization by ETO. Phillips and Hoffman (7) reported that viable microorganisms could be recovered from the interior of some electronic components. Angelotti (*unpublished data*) found that microorganisms enclosed in plastic were 5 to 30 times more resistant to dry heat than unprotected microorganisms. Other investigators (2, 6) also demonstrated increased resistance to dry heat sterilization of spores in various types of solid materials. In a recent paper, Doyle and Ernst (3) reported that spores occluded in water-insoluble crystals of calcium carbonate were not sterilized by exposure to ETO and were 900 times more resistant to moist heat and 9 times more resistant to dry heat than unoccluded spores. They concluded that poor heat transfer within the crystal was the most likely explanation for the increased resistance to dry heat.

The primary purpose of this study was to determine the resistance of spores included within water-soluble crystals to dry heat at 125 C and to a gaseous mixture of methyl bromide (MeBr) plus ETO and ETO alone at 25 C.

Glycine and NaCl were selected as organic and inorganic crystals that met the following criteria: (i) melting point above 200 C, (ii) no water of crystallization, and (iii) moderate-sized crystals (1 mm or larger) readily formed.

MATERIALS AND M

Preparation of crystals con spores of *Bacillus subtilis* var. *ni* sterile distilled water to give a 10⁸ viable spores per ml. A satu cine or NaCl was prepared with at 56 C and held in a water bath ture. The spore suspension (1 saturated solution were pipette petri dish and were mixed by covered dish was placed in a 37 tals were harvested when they l size (generally after 1 to 3 days the holding period, the dish wa daily to resuspend settled spor were blotted on tissue paper a dishes at room temperature ur

Glycine crystals used in the from 2 × 1 × 1 mm (0.003 g) t g). Viable spores recovered fr washing to remove surface from approximately 1,000 to 9 about 100,000. NaCl crystals r 1 × 1 mm (<0.005 g) to 7 × Viable spores recovered, after 300 to 9,000 with a mean of at an exposed cytstal was matche by weight and size with an un The wide range in crystal siz cluded spores complicates dir results.

Clean glass microscope slid 0.01 ml of the spore suspensi 10⁶ spores per slide) and drie viable spor from these slid recovery from the crystals.

Exposure of crystals with er and glass slides in an open pe forced-draft electric oven whic about 127 C. During the inse oven temperature usually dro then required 2 to 4 min to re the exposure period was sta ranged from 2 to 24 hr at 12

Crystals containing spores sterilants were placed on a gal in a vacuum-type desiccator scribed and illustrated by Gi system, relative humidity (R justed, a partial vacuum is c sterilizing gas is introduce within the jar almost up to

Crystals of glycine or Na spores were exposed to a MeBr and 60% ETO, by vol liter and 642 mg of ETO per ties above 75% at 25 C for high RH was obtained by pl wet with distilled water into

Glycine and NaCl crysta gaseous ETO at low (35 t humidities for 24 to 48 hr a ETO ranged from 140 to 642

Vol. 16, No. 8
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MATERIALS AND METHODS

Preparation of crystals containing spores. Dry spores of *Bacillus subtilis* var. *niger* were suspended in sterile distilled water to give a concentration of 8×10^8 viable spores per ml. A saturated solution of glycine or NaCl was prepared with sterile distilled water at 56 C and held in a water bath at the same temperature. The spore suspension (1 ml) and 9 ml of the saturated solution were pipetted into a sterile 50-mm petri dish and were mixed by swirling the dish. The covered dish was placed in a 37 C incubator, and crystals were harvested when they had reached a suitable size (generally after 1 to 3 days of incubation). During the holding period, the dish was swirled at least once daily to resuspend settled spores. At harvest, crystals were blotted on tissue paper and held in closed petri dishes at room temperature until used.

Glycine crystals used in these tests ranged in size from $2 \times 1 \times 1$ mm (0.003 g) to $12 \times 9 \times 3$ mm (0.32 g). Viable spores recovered from these crystals, after washing to remove surface contaminants, ranged from approximately 1,000 to 900,000 with a mean of about 100,000. NaCl crystals ranged in size from $1 \times 1 \times 1$ mm (<0.005 g) to $7 \times 4 \times 3$ mm (0.175 g). Viable spores recovered, after washing, ranged from 300 to 9,000 with a mean of about 3,000. In each test, an exposed cytstal was matched as closely as possible by weight and size with an unexposed control crystal. The wide range in crystal sizes and numbers of included spores complicates direct comparisons of test results.

Clean glass microscope slides were inoculated with 0.01 ml of the spore suspension (approximately 8×10^6 spores per slide) and dried at 25 C. Recovery of viable spores from these slides was compared with recovery from the crystals.

Exposure of crystals with entrapped spores. Crystals and glass slides in an open petri dish were placed in a forced-draft electric oven which had been preheated at about 127 C. During the insertion of the crystals, the oven temperature usually dropped to about 121 C and then required 2 to 4 min to reach 125 C, at which time the exposure period was started. The exposure time ranged from 2 to 24 hr at 125 C.

Crystals containing spores to be exposed to gaseous sterilants were placed on a galvanized wire mesh screen in a vacuum-type desiccator jar similar to that described and illustrated by Gilbert et al. (4). With this system, relative humidity (RH) within the jar is adjusted, a partial vacuum is drawn in the jar, and the sterilizing gas is introduced, bringing the pressure within the jar almost up to atmospheric pressure.

Crystals of glycine or NaCl containing entrapped spores were exposed to a gaseous mixture of 40% MeBr and 60% ETO, by volume (964 mg of MeBr per liter and 642 mg of ETO per liter), at relative humidities above 75% at 25 C for 48 hr. In these tests, the high RH was obtained by placing a filter paper patch wet with distilled water into the sealed jar.

Glycine and NaCl crystals were also exposed to gaseous ETO at low (35 to 38%) and high relative humidities for 24 to 48 hr at 25 C. Concentrations of ETO ranged from 140 to 642 mg/liter.

Filter paper or cotton twill patches, each containing a dried inoculum of approximately 1 million spores, were compared with the crystals in these tests.

Exposure of spores on surface of crystals to gaseous ETO. Crystals of NaCl were either held at ambient (room) RH or dried at $< 1\%$ RH; then the surfaces of the crystals were grossly contaminated by rolling the crystals in a powder of dry spores (5×10^{11} viable spores per g) of *B. subtilis* var. *niger*. These crystals were exposed to ETO (319 to 362 mg/liter) at either 34 or 42% RH at 25 C for 24 hr.

Filter paper or cotton twill patches containing dried spores were exposed with the crystals in some tests.

Assay of viable spores. After exposure of the single crystals to either dry heat or gaseous sterilants, each crystal was aseptically transferred to a rubber-stoppered test tube containing sterile distilled water. Glass slides were aseptically transferred to bottles containing a sterile aqueous 0.01% solution of Tween 20 and were shaken for 5 min on a mechanical shaker. Unexposed (control) crystals were washed by swirling for about 1 min in sterile distilled water and rinsed in 100% ethyl alcohol before dissolving and sampling. Washing the unexposed crystals was designed to eliminate or drastically reduce the number of viable spores on the crystal surface so that essentially only spores within the crystal would remain. The washing procedure removed some of the surface layer of the crystals including some of the spores entrapped there.

After washing, each single control crystal was dissolved in a test tube containing sterile distilled water. In tests where filter paper or cotton twill patches containing spores were used for comparison, each patch was placed into a test tube containing 9.0 ml of sterile distilled water. Immediately prior to plating, each tube was vigorously shaken by hand.

Plate Count Agar (Difco) was used as the assay medium for viable spores in all tests. The pour plate method of assaying for viable spores was employed. All plates were incubated at 36 C for 48 hr before counting.

RESULTS

Recovery of viable spores from the interior of crystals exposed to dry heat at 125 C. Viable spores were consistently recovered from large glycine crystals heated at 125 C for periods up to and including 20 hr, but no viable spores were recovered after exposure for 24 hr. Recoveries from glycine crystals of various sizes after exposures of 2 to 20 hr at 125 C gave D values ranging from more than 1 to 6 hr, when compared with recoveries from unheated washed crystals.

Crystals of NaCl yielded viable spores after heating at 125 C for 4 hr or less, but no viable spores were recovered from NaCl crystals after 16 hr or longer. Calculated D values for spores heated in NaCl crystals at 125 C are generally in the range of 1 to 2 hr.

Table 1 presents the mean percentage of survival of spores in glycine and NaCl crystals exposed to dry heat at 125 C. Recovery of viable

TABLE 1. *Mean percentage of survival of viable spores of B. subtilis var. niger from crystals heated at 125 C*

Time of heating at 125 C	Crystal wt	Glycine crystals		NaCl crystals	
		Survival	*D* values	Survival	*D* values
hr	*t*	%	*hr*	%	*hr*
2	<0.01	4	1.4	5	1.5
	0.01–0.09	10	2.0	—	
	0.10–0.32	19	2.8	—	
4	<0.01	—	—	0	
	0.01–0.09	0.1	1.3	0.3	1.6
16	<0.01	0.2	5.8	—	
	0.01–0.09	—	—	0	
18	0.01–0.09	0.001	3.6	—	
	0.10–0.32	—	—	0	
20	0.10–0.32	0.05	6.0	—	
24	0.01–0.09	0		—	
	0.10–0.32	0		0	

TABLE 2. *Recovery of viable spores from glycine crystals of various sizes*

Crystal wt	Mean viable spores recovered from glycine crystals		Percentage survival[a]	*D* values
	Heated at 125 C for 2 hr	Unheated (washed) crystals		
t				*hr*
<0.01	270	7,400	4	1.4
0.01–0.09	2,300	22,000	10	2.0
0.10–0.32	28,000	147,000	19	2.8

[a] Percentage survival = 100 × heated/unheated.

spores from a glass slide heated at 125 C for 30 min was about 0.8%, which gives a *D* value of about 15 min. With one exception, no viable spores were recovered from glass slides exposed to 125 C for 1 hr or longer in repeated tests.

Crystal size is apparently a factor in recovery of viable spores from heated crystals, with the greater number of spores generally recovered from the larger crystals and the percentage of recovery also generally higher from larger crystals. These relationships are given in Table 2 for glycine crystals heated at 125 C for 2 hr.

Recovery of viable spores from the interior of crystals after exposure to sterilizing gases. Crystals of glycine or NaCl containing enclosed spores showed no reduction in viable spore counts after exposure to a gaseous MeBr-ETO mixture or gaseous ETO at about 37% RH at 25 C for up to 48 hr as compared with unexposed washed crystals. However, NaCl crystals exposed at high RH (>75%) to MeBr plus ETO or ETO alone for 48 hr either partially or completely dissolved and were either sterile or yielded only low numbers of viable spores upon assay.

Recovery of viable spores from the surfaces of crystals exposed to ETO. Surfaces of NaCl crystals, grossly contaminated with more than 10^7 viable spores by tumbling in a powder of dry spores, were generally sterilized when exposed to gaseous ETO at 34 or 42% RH for 24 hr at 25 C.

DISCUSSION

Spores included in glycine crystals were 5 to 24 times more resistant to dry heat than unprotected spores, and spores included in NaCl crystals were about 6 times more resistant. The apparent greater resistance of spores in glycine crystals over spores in NaCl crystals was probably due to the larger average size of the glycine crystals and not the chemical. The ninefold increase in dry-heat resistance of spores in water-insoluble crystals over nonprotected spores reported by Doyle and Ernst (3) is within the range of the increase in resistance of 5 to 24 times reported here for spores protected by water-soluble crystals of various sizes. This similarity is rather interesting considering the numerous differences between the test procedures, such as (i) use of water-soluble crystals versus water-insoluble crystals, (ii) heated in oven at 125 C versus heated in special aluminum block at 121 C, (iii) crystals 1 to 12 mm versus crystals considerably smaller than 1 mm, (iv) crystals formed rather slowly versus crystals formed rapidly, and (v) crystals dried at room temperature versus crystals dried at 90 C.

Interest in the MeBr-ETO mixture was enhanced by reports of a synergistic effect with these two gases by Richardson and Monro (8) and more recently by Russian representatives at the meetings of the Committee on Space Research in Vienna in May 1966 (10). However, exposure of water-soluble crystals to a gaseous mixture of MeBr and ETO (40% MeBr + 60% ETO by volume) did not kill spores within the crystals any more successfully than did ETO alone. Because ETO gas can penetrate some organic materials, such as various plastics and rubber, the glycine was used here to test the ability of the MeBr-ETO mixture and ETO alone to penetrate and kill spores within an organic crystal.

The inability to sterilize spores in crystals of glycine or NaCl by gaseous ETO agrees with similar observations in previous reports: Doyle and Ernst (3) with water-insoluble crystals, and Abbott, Cockton, and Jones (1) with crystals of Rochelle salt (and glycine crystals exposed to formaldehyde).

The protective effect provided against gaseous sterilization of spores entrapped in crystals is

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probably caused by the inability of the gas molecule to penetrate the crystal lattice rather than competition for the gas between the crystalline material and the embedded spores.

The surfaces of NaCl crystals grossly contaminated with more than 10^7 viable spores were sterilized by exposure to gaseous ETO when the gas concentration, RH, and exposure time were adequate.

Doyle and Ernst (3) discussed several possible explanations for the increased resistance to dry heat of spores in crystals and concluded that poor heat transfer within the crystal was the most probable reason. Angelotti (*unpublished data*) thought that the protective effect against dry heat provided by embedding spores in solids was most plausibly explained by the prevention of spore desiccation. We believe that moisture is a factor in the increased resistance of entrapped spores, but investigations to date have not shown the precise nature of this role.

Because natural crystals in soils and elsewhere probably contain viable trapped spores, additional information on the resistance of these spores to sterilization should be of interest, especially in areas where the labile nature of the materials limits the choice of sterilization methods and there is a critical sterility requirement such as with planetary probes or drugs.

ACKNOWLEDGMENT

Crystals used during the early phases of this investigation were grown by Charles Borland, and his method of growing the crystals was used throughout this study.

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Exhibit S

Establishment of limits for content and related foreign steroids in budesonide substance

During the development work with budesonide substance we have used pharmacopeial monographs for other steroid substances (see enclosure 1) as guideline in the evaluation of quality and in the establishment of limits.

In addition we had the intention to work out analysis methods for budesonide with a very high degree of selectivity and sensitivity for related foreign steroids. These requirements are fulfilled by the control method, which is used for the analysis of budesonide substance: The high selectivity can be illustrated by the total separation of the two epimers of budesonide, when using HPLC. Using TLC the separation of the epimers is not possible. With a detection limit of about 0.01% the HPLC method is highly superior to TLC even concerning sensitivity. This efficient analysis method together with the fact that repeated recrystallization of budesonide is not possible (the epimer ratio would be changed considerably) made it necessary to establish initially a 95-103% limit for the content of drug substance.

Analytical data for all small scale production batches of budesonide used for different purposes during the development work are given in enclosures 2 and 3.

If this experience of small scale production can be extended to large scale production it would be reasonable to tighten the limits for the assay to 96-102%; by that the lower limit would correspond to the limits allowed in monographs for steroids in Ph.Eur.. However, to avoid limits that could not be met when manufacture is undertaken on a production scale (1 kg or more) we need 5-10 such batches for a revision of the assay limits to an appropriate figure.

Related foreign steroids are determined by calculating relative peak areas in the HPLC chromatograms, which is illustrated in the examples in enclosures 4 and 5. For this determination in principle the same HPLC-system is used as for the budesonide assay (encl. 4 and 5). With the experience of full scale production a revision to 4% for the maximum amount of related foreign steroids would be a natural complement to a 96% limit.

800326/G Roth/ANi

Limits for content and related foreign steroids in pharmacopeial monographs for different steroid substances

USP XIX

Topical steroids are normally assayed by a UV-measurement after a separation by TLC. With this fairly selective analysis method limits for steroid content are in most cases 97-102% or 97-103%. A special test for related foreign steroids is usually not performed.

BP 73 and Ph.Eur.

The steroid content is normally determined by a direct UV-measurement or by a spectrophotometric determination after reaction with blue tetrazolium reagent. With this rather unselective analysis method the most frequent content limits are 96-104% and in some cases 97-103%. Normally a complementary test for related foreign steroids is performed by TLC. No definite limit for the maximally allowed total amount of related foreign steroids is given. The detection limit for related foreign steroids with this test is about 1%.

800326/G Roth/ANi

Assay for all small scale production batches of budesonide.

Batch	Content (%)	Comments
1/76	97.9	
2/76	98.6	
18/77	92.2	Not approved
22/77	99.2	
23/77	98.7	
24/77	98.6	
33/77	98.9	
34/77	98.4	
35/77	98.7	
39/78	99.1	
41/78	97.4	
42/78	97.0	
47/78	95.1	Not approved
48/78	94.6	Not approved
52/78	98.1	
54/78	98.6	
55/78	98.7	
62/79	99.0	
63/79	99.5	
64/79	99.6	
65/79	98.4	
66/79	97.4	

800326/G Roth/ANi

Amount "related foreign steroids" in small scale production batches of budesonide.

Batch	Related foreign steroids (%)
1/76	2.1
2/76	1.0
22/77	1.2
23/77	1.1
24/77	1.0
33/77	1.3
34/77	1.2
35/77	1.0
39/78	1.2
41/78	2.2
42/78	2.5
52/78	2.3
54/78	1.1
55/78	1.2
62/79	1.2
63/79	1.8
64/79	1.6
65/79	1.7
66/79	0.7

800326/G Roth/ANi

Exhibit T

Limits for content and related foreign steroids in budesonide substance

In connection with the registration application for Preferid ointment 0.025% (Dsp nr 3802) discussion was held between Sundhetsstyrelsen and AB Draco concerning the content and related foreign steroids in budesonide substance (our letter 800327 EB/bk).

As a result of this discussion the following limits were agreed upon:

Content: 96-102%
Related foreign steroids: maximum 4%

Reevaluation of the limits is to be done after some time of large scale production. (Your letter dated 800401 SK/AKr).

801104/ET/AHn

T. Dammark

Residue of ethylene oxide

The residue of ethylene oxide has been determined in three batches of budesonide micronized sterile substance. These lots were used for the first production batches of Preferid cream, which are intended for marketing purposes.

Analysis method

The ethylene oxide residue has been determined by gas ghromatography with a FID-detector after dissolution of budesonide micronized sterile substance in chloroform.

Results

Batch DFC	107	12 µg ethylene oxide/g substance
"-	108 (bottle 3)	19 "-
"-	108 (bottle 4)	22 "-

Comments and conclusion

A low ethylene oxide content is observed. At an ethylene oxide residue of 25 ppm in the budesonide substance the ethylene oxide content in the cream preparation would be about 0.006 ppm. In our opinion, figures of this magnitude do not justify establishment of limits and routine analysis for ethylene oxide.

801104/GR/AHn

Exhibit U1

Analys begärd den	Färdig senast den	Beställare	Projekt nr
800815		LENNART WENNGREN	850-31

Önskad undersökning	Provmärkning
	22-134-11
Enligt specifikation nr H-B-29-1-I	BUDESONID MIKRO STERIL
	Batch DFC 107

Kort redogörelse för den frågeställning som ligger till grund för analysbegäran

Resultat

1. Utseende: v.g.
2. IR-kurva: överensstämmer med ref. substans
3. Torkförlust: 0.1 %
4. Främmande steroider: 1.5 %
5. Epimer A: 48.1 %
6. Budesonid: 97.7 % (enhalt ...)
7. Sterilitet: ingen växt

Analysprotokoll nr 80-2786

AB Draco

den 800828

Sign:

DRACO

Analytical certificate

Analysis asked for	Ready at the latest	Customer	Project no
800815	?	LENNART WENNGREN	850-31

Desired investigation

According to specification
no H-B-29-1-I

Sample marking

22-134-11
Budesonide micro sterile
Batch DFC 107

Short report of the problem being the reason for the analysis request

Results

1. Appearance:	Without remark
2. IR-curve:	Conform to reference curve
3. Loss on drying:	0.1 %
4. Foreign steroids:	1.5 %
5. Epimer A:	48.1 %
6. Budesonide:	99.7 %, calculated on dry sample
7. Sterility:	No growth

Analytical record: 80-0786

AB Draco

on the 800828

Sign: BP EB

Exhibit U2

DRACO

Analysintyg

Analys begärd den	Färdig senast den	Beställare	Projekt nr
1978 09 07	1978 09 15	M. Pålsson	850-11

Önskad undersökning
halt S-1320
renhet
isomer fördelning

Provmärkning
Budesonide mikro
Batch MP4

Kort redogörelse för den frågeställning som ligger till grund för analysbegäran

Provet lämnas i 2 burkar
Före mikronisering hade substansen beteckningen Batch 33/77

Resultat

Isomer fördelning : 52,5 % S-1322
47,5 % S-1321

Föroreningar C_{18}-kolonn: 0,6 %

Halt Budesonide: 98,9 % (Dubbelprov! Ett prov ur varje burk.)

Föroreningar NH_2-kolonn: 0,5 %

Analysprotokoll nr 78-0497

AB Draco

den 780914

Sign:

SR. BF

Kopior i Lund 751030

DRACO

Analytical certificate

Analysis asked for	Ready by the latest	Customer	Project no
19780907	19780915	M. Pålsson	850-11

Desired investigation

Content S-1320
Purity
Isomer distribution

Sample marking

Budesonide micro
Batch MP4

Short report of the problem being the reason for the analysis request

The sample is delivered in two pots
Before micronization the substance had the designation: Batch 33/77

Results

Isomer distribution:	52.5 %	S-1322
	47.5 %	S-1321

Impurities C_{18} column: 0.6 %

Content budesonide: 98.9 % (Double sample! One sample from each pot)

Impurities NH_2 column: 0.5 %

Analytical record: 78-0497

AB Draco

on the 780914

Sign: GR BP

Exhibit U3

DRACO

Analysintyg

Analys begärd den	Färdig senast den	Beställare	Projekt nr
800211		LENNART WENNGREN	850-31

Önskad undersökning	Provmärkning
Halt BUDESONID	22-134-11
Föroreningar	BUDESONID mikro 'steril
	Batch DFB 101

Kort redogörelse för den frågeställning som ligger till grund för analysbegäran

Godkänd 22-133-12 Budesonid mikro Batch DFB 1 som etylenoxid steriliseras . (GAMBRO)

Temperatur: 55°C, tid: 4 timmar.

Resultat

Halt: 99,4 % budesonid

Föroreningar 1,1 %

Analysprotokoll nr 80-0156

AB Draco

den 800228

Sign: BB

DRACO

Analytical certificate

Analysis asked for	Ready at the latest	Customer	Project no
800211		LENNART WENNGREN	850-31

Desired investigation

Content Budesonide
Impurities

Sample marking

22-134-11
Budesonide micro sterile
Batch DFB 101

Short report of the problem being the reason for the analysis request

Approved 22-133-12 Budesonide micro Batch DFB 1 being ethylene oxide sterilized (GAMBRO)
Temperature: 55°C, time: 4 hours

Results

Content:	99.4 % budesonide
Impurities:	1.1 %

Analytical record: 80-0156

AB Draco

on the 800228

Sign: EB

Exhibit U4

draco

Analysintyg

Analys begärd den	Färdig senast den	Beställare	Projekt nr
800204		LENNART WENNGREN	850-31

Önskad undersökning	Provmärkning
	22-133-12
Enligt internspecifikation nr	BUDESONID mikroniserad
H-B-28-1-I	Batch DFB 1

Kort redogörelse för den frågeställning som ligger till grund för analysbegäran

Utgångs substans: 22-122-15 Budesonid batch 11P

Resultat

1. Utseende : u.a.
2. IR-kurva Stämmer med referens kurva
3. Torkförlust 0,1 %
4. Främmande steroider 1,0 %
5. Epimer A 48,9 %
6. Budesonid : 99,6 % räknat på ursprungligt prov
7. Partikelstolek : Godkänd
8. Mikrobiologiskt skick Godkänd

Analysprotokoll nr 80-0154

AB Draco

den 800228

Sign: EB

DRACO

Analytical certificate

Analysis asked for	Ready at the latest	Customer	Project no
800204		LENNART WENNGREN	850-31

Desired investigation

According to internal specification
No H-B-28-1-I

Sample marking

22-133-12
Budesonide micronized
Batch DFB 1

Short report of the problem being the reason for the analysis request

Starting substance: 22-122-15 Budesonide batch 11P

Results

1. Appearance:	Without remark
2. IR-curve:	In accordance with reference curve
3. Loss on drying:	0.1 %
4. Foreign steroids:	1.0 %
5. Epimer A:	48.9 %
6. Budesonide:	99.6 %, calculated on original sample
7. Particle size:	Approved
8. Microbiological condition:	Approved

Analytical record: 80-0154

AB Draco

on the 800228

Sign: EB

DRACO

Exhibit U5

Analysintyg

Analys begärd den	Färdig senast den	Beställare	Projekt nr
800318		LENNART WENNGREN	850-31

Önskad undersökning

Enligt internspecifikation nr

H-B-29-1-I

Provmärkning

BUDESONID mikro steril

Batch DFC 104

Kort redogörelse för den frågeställning som ligger till grund för analysbegäran

Budesonid batch 41/78 - Budesonid mikro batch DFB2

Etylenoxidsteriliserad (GAMBRO)

Resultat

1. Utseende: Substansen har klumpat ihop sig.
2. IR-kurva: Överensstämmer med referensdiagram
3. Torkförlust: 0,15 %
4. Främmande steroider: C18-kolonn: 0,9 % NH2-kolonn: 1,3 %
5. Epimer A: 47,1 %
6. Budesonid: 97,1 %
7. Sterilitet: Ingen växt

800328 Substansen skall ej skickas till Japan

e.i samtal SHg, JW, LW, EB.

Analysprotokoll nr 90-1,329

AB Draco

den 800328

Sign:

DRACO

Analytical certificate

Analysis asked for	Ready at the latest	Customer	Project no
800318		LENNART WENNGREN	850-31

Desired investigation

According to internal specification
no H-B-29-1-I

Sample marking

Budesonide micro sterile
Batch DFC 104

Short report of the problem being the reason for the analysis request

Budesonide batch 41/78 – Budesonide micro batch DFB2
Ethylene oxide sterilized (GAMBRO)

Results

1. Appearance:	The substance has formed lumps	
2. IR-curve:	Conform to reference curve	
3. Loss on drying:	0.15 %	
4. Foreign steroids:	C_{18}-column: 0.9 %	NH_2-column: 1.3 %
5. Epimer A:	47.1 %	
6. Budesonide:	97.1 %	
7. Sterility:	No growth	

800328. The substance should not be sent to Japan in accordance with conversation with SHg, IW, LW, EB.

Analytical record: 80-0329

AB Draco

on the 800328

Sign: BP EB

DRACO

Analysintyg

Exhibit U6

Analys begärd den	Färdig senast den	Beställare	Projekt nr
800318		LENNART WENNGREN	850-31

Önskad undersökning	Provmärkning
Enligt internspecifikation nr H-B-29-1-I	BUDESONID mikro steril Batch DFC 105

Kort redogörelse för den frågeställning som ligger till grund för analysbegäran

Substansen skall sändas till FUJISAWA Japan.

Budesonid batch 11P - Budesonid mikro batch DFB 1

Etylenoxidsteriliserad (GAMBRO)

Resultat

1. Utseende : Substansen har klumpat ihop sig
2. IR-kurva Överensstämmer med referensdiagram
3. Torkförlust 0,13 %
4. Främmande steroider Eq-kolonn 0,4 % NH_2-kolonn: 0,5 %
5. Epimer A : 48,2 %
6. Budesonid : 99,0 %
7. Sterilitet Ingen växt

Analysprotokoll nr 89-0330

AB Draco

den 900328

Sign: BP EB

DRACO

Analytical certificate

Analysis asked for	Ready at the latest	Customer	Project no
800318		LENNART WENNGREN	850-31

Desired investigation

According to internal specification
no H-B-29-1-I

Sample marking

Budesonide micro sterile
Batch DFC 105

Short report of the problem being the reason for the analysis request

The substance should be sent to FUJISAWA Japan

Budesonide batch 11P – Budesonide micro batch DFB1
Ethylene oxide sterilized (GAMBRO)

Results

1. Appearance:	The substance has formed lumps	
2. IR-curve:	Conform to reference curve	
3. Loss on drying:	0.13 %	
4. Foreign steroids:	C_{18}-column: 0.4 %	NH_2-column: 0.5 %
5. Epimer A:	48.2 %	
6. Budesonide:	99.0 %	
7. Sterility:	No growth	

Analytical record: 80-0330

AB Draco

on the 800328

Sign: BP EB

DRACO

Analysintyg

Exhibit U7

Analys begärd den	Färdig senast den	Beställare	Projekt nr
800513		L. Wennglen	850 - 31

Önskad undersökning	Provmärkning
Halt Budesonid ~~Endotoxinhalt~~ ~~Fetthalt~~	Budesonid mikro steril batch DFE 109

Kort redogörelse för den frågeställning som ligger till grund för analysbegäran

Godkänd Budesonid mikroniserad, som har ethylenoxidsteriliserat av AB Medeh Produkter.

Resultat

98,5 %

Substansen är mycket svårhanterlig, då den är statiskt laddad.

Analysprotokoll nr 80-3485

AB Draco

den 800613

Sign: [illegible]

DRACO

Analytical certificate

Analysis asked for	Ready at the latest	Customer	Project no
800513		L. Wenngren	850-31

Desired investigation

Content Budesonide

Sample marking

Budesonide micro sterile
Batch DFE 109

Short report of the problem being the reason for the analysis request

Approved Budesonide micronized being ethylene oxide sterilized by AB Medett products

Results

98.5 %

The substance is very difficult to handle due to static charged

Analytical record: 80-0485

AB Draco

on the 800609

Sign: BP

Exhibit U8

DRACO

Analysintyg

Analys begärd den	Färdig senast den	Beställare	Projekt nr
1979-05-04		LENNART NYMGREN	850-2

Önskad undersökning	Provmärkning
Identity	
Content of Budesonide	
Epimer A	Micronized Budesonide (S-1320)
Related foreign steroids	Batch 790319

Kort redogörelse för den frågeställning som ligger till grund för analysbegäran

Budesonid batch 790112 mikroniserad 3gr.

Resultat

Identity: positive (HPLC)

Content of Budesonide: 98.6%

Epimer A: 46.9%

Related foreign steroids: ~ 0.5%

Analysprotokoll nr 79-0333

AB Draco

den

Sign:

DRACO

Analytical certificate

Analytical certificate

Analysis asked for	Ready at the latest	Customer	Project no
1979-05-04		LENNART WENNGREN	850-31

Desired investigation

Identity
Content of Budesonide
Epimer A
Related foreign steroids

Sample marking

Micronized Budesonide (S-1320)
Batch 790319

Short report of the problem being the reason for the analysis request

Budesonide batch 790112 micronized 3 times

Results

Identity:	Positive (HPLC)
Content of Budesonide:	98.6 %
Epimer A:	46.9 %
Related foreign steroids:	about 0.5 %

Analytical record: 79-0333

AB Draco

on the 790504

Sign:

DRACO TRANSLATION OF ANALYTICAL CERTIFICATE Analyscintyg

Exhibit U9

Analys begärd den	Färdig senast den	Beställare	Projekt nr

Önskad undersökning	Provmärkning
Investigation required:	
According to specification for	BUDESONIDE micronized batch 790319
BUDESONIDE micronized H-B-28-1-I	

Kort redogörelse för den frågeställning som ligger till grund för analysbegäran

Resultat

Results:

Appearence: White to off-white fine powder

IR-Spectrum: Conform to a reference Spectrum

Particle size : 50% (w/w) $\leq$ 3 µm and 90% (w/w) $\leq$ 7 µm

Analysprotokoll nr
79-0333

AB Draco

den 790504

Sign: BP EB

DRACO

Analytical certificate

TRANSLATION OF ANALYTICAL CERTIFICATE

Analysis asked for	Ready at the latest	Customer	Project no

Desired investigation

Investigation required:
According to specification for
Budesonide micronized H-B-28-1-I

Sample marking

Budesonide micronized batch 790319

Short report of the problem being the reason for the analysis request

Results

Results:

Appearance:	White to off-white fine powder
IR-spectrum:	Conform to a reference Spectrum
Particle size:	50 % (w/w) ≤ 3 µm and 90 % (w/w) ≤ 7 µm

Analytical record: 79-0333

AB Draco

on the 790504

Sign: BP EB

Exhibit U10

DRACO — Analysbeställning

Analys begärd den	Färdig senast den	Beställare	Projekt nr
790504		Lennart Wennergren	850 - 31

Önskad undersökning

~~HPLC~~

IDENTITET BUDESONID

Provmärkning

BUDESONIDE MIKRONISERAD

Batch 790319

(EtO-steriliserad Gambro 790412

Kort redogörelse för den frågeställning som ligger till grund för analysbegäran

Provet har tagits från etylenoxid steriliserad Budesonide mikro, som skall användas till Budesonide 0,025 % kräm. Tillverkning i Södertälje. 250 kg.

Resultat

Identitet: POSITIV (överensstämmer med referenskurva)

Analysprotokoll 79-85 sv

AB Draco

den 790508

Sign: EB

DRACO

Analytical certificate

Analysis asked for	Ready at the latest	Customer	Project no
790504		Lennart Wenngren	850-31

Desired investigation

Identity Budesonide

Sample marking

Budesonide micronized
Batch 790319
(EthO-sterilized Gambro 790427)

Short report of the problem being the reason for the analysis request

The sample has been taken from ethylene oxide sterlized Budesonide micro, which would be used to Budesonide 0.025 % cream. Manufacturing in Södertälje. 250 kg

Results

Identity: Positive (conform to reference curve)

Analytical record: 79-0347

AB Draco

on the 790508

Sign: EB BP

Exhibit U11

DRACO

Analysbegärd den	Färdig senast den	Beställare	Projekt nr
781207	781208	L. Hennigren	

Önskad undersökning	Provmärkning
Halt Budesonide	Budesonide, mikroniserad
Renhet C_{18}, NH_2-kolonn	Batch MP4
	Etylenoxidsterilisering
	(Gambro) 781121

Kort redogörelse för den frågeställning som ligger till grund för analysbegäran

Resultat

Halt Budesonide: 98,9 %

Renhet C_{18}-kolonn: ~1,1 %

– " – NH_2-kolonn: ~0,5 %

Isomerfördelning: Epimer A 47,7 %

– " – B 52,3 %

Analysprotokoll nr 78-0710

AB Draco

den 781212

Sign:

DRACO

Analytical certificate

Analysis asked for	Ready at the latest	Customer	Project no
781207	781208	L. Wenngren	

Desired investigation

Content Budesonide
Purity C_{18}, NH_2-column

Sample marking

Budesonide micronized
Batch MP4
Ethylene oxide sterilized
(Gambro) 781121

Short report of the problem being the reason for the analysis request

Results

Content Budesonide:	98.9 %	
Purity C_{18}-column:	about 1.1 %	
Purity NH_2-column:	about 0.5 %	
Isomer distribution:	Epimer A	47.7 %
	Epimer B	52.3 %

Analytical record: 78-0710

AB Draco

on the 781212

Sign: ? BP